Medical Discoveries

VOLUME 1 A C

Medical Breakthroughs and the People Who Developed Them

Bridget Travers and
Fran Locher Freiman, Editors

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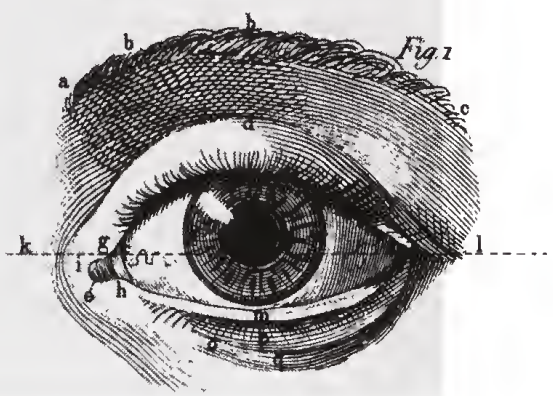
Volume 1: A-C



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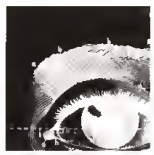

Reader's Guide

Medical Discoveries: Medical Breakthroughs and the People Who Developed Them features 215 entries on medical and dental inventions and discoveries that have had a great impact on health throughout the world—from fluoride treatments to AIDS therapies—as well as the people responsible for them. Written in nontechnical language, *Medical Discoveries* explores medical practices such as acupuncture, significant developments in research such as chemotherapy, and instrumentation such as X-ray machines that have profoundly changed the way diseases are diagnosed and people are treated.

Each *Medical Discoveries* entry, whether on a well-known discovery or a lesser-known invention, identifies the person behind the breakthrough, explores the knowledge and technology that led to it, and explains how the advance changed the world in which we live.

Scope

Arranged alphabetically over three volumes, *Medical Discoveries*'s entries range from one-quarter to seven pages in length. Accompanying several of the entries are sidebar boxes discussing related topics and items of special interest to students, such as the discovery of DNA structure. Boldfaced terms in entry text direct the reader to related entries in the set. Cross-references at the end of an entry direct the reader to related breakthroughs and discoveries not specifically mentioned in that entry. More than 150 photographs enliven and help explain the text.

Each *Medical Discoveries* volume opens with a further readings page that guides readers to titles of similar interest, a timeline of medical and dental landmarks, and a glossary of important medical and dental terms found in the text. The volumes conclude with a comprehensive gen-

eral index, providing easy access to the people, theories, and discoveries and inventions mentioned throughout *Medical Discoveries.*

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Comments and Suggestions

We welcome your comments on this work as well as your suggestions for topics to be featured in future editions of *Medical Discoveries: Medical Breakthroughs and the People Who Developed Them.* Please write: Editors, *Medical Discoveries,* U·X·L, 835 Penobscot Bldg., Detroit, Michigan 48226-4094; call toll-free: 1-800-877-4253; or fax 1-313-877-6348.

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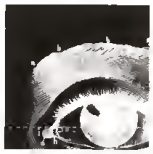

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Timeline of Medical Events

4000 B.C.: Babylonians use opium in medical procedures.

3000 B.C.: First recorded cesarean surgeries are performed in Egypt.

762 B.C.: Wang Ping compiles an edition of the *Nei Ching*, a basic reference book on acupuncture.

700 B.C.: Etruscans construct false teeth from ivory and bone.

c. 600 B.C.: Skin graft surgery is successfully performed in India.

c. 400 B.C.: Hippocrates studies how disease is spread from person to person.

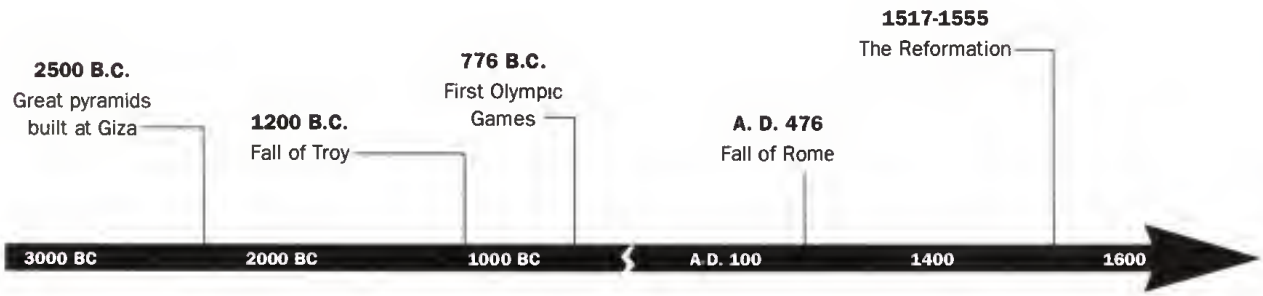
c. A.D. 160: Galen conducts extensive studies of animal anatomy.

1285: Salvino degli Armati invents eyeglasses.

1492: Pope Innocent VIII receives the first recorded blood transfusion.

1536: Surgeon Ambroise Paré designs the first artificial limbs.

1543: Anatomist Andreas Vesalius publishes his influential medical text about the human body called *De humani corporis fabrica*.



Early 1600s: Bristle-style toothbrush is introduced in Europe.

1616: Dr. William Harvey lectures about blood circulation.

1748: J. Daviel performs the first cataract operation.

1792: Dominique-Jean Larrey begins the first field ambulance service.

1796: Edward Jenner develops the smallpox vaccine.

1816: Rene Theophile Laennec invents the modern stethoscope.

1818: Humphry Davy discovers nitrous oxide, or "laughing gas."

1835: Theodor Schwann uncovers pepsin in gastric juice.

c. 1850s: Louis Pasteur develops the theory that germs cause disease by interfering with the body's biological processes.

1852: Antonius Mathijsen develops plaster of paris casts for setting fractures.

1853: Charles Pravaz invents the hypodermic syringe.

1865: Joseph Lister introduces antiseptic surgical procedures.

1866: Sir Thomas Clifford Allbutt invents the medical thermometer.

1866: Pasteurization is first used prevent wine spoilage.

1876: Siegfried von Basch invents the modern blood pressure measuring device.

1879: Listerine is introduced as a patent medicine.

1880: Gregor Mendel discovers hereditary factors in plants.

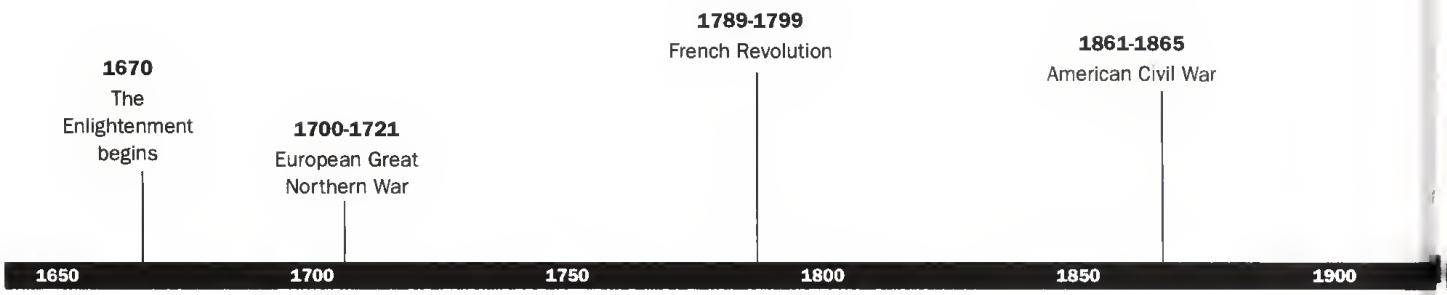
c. 1880: Elie Metchnikoff discovers the role white blood cells play in disease control.

1888: Eugene Kalt develops first contact lens.

1895: Wilhelm Roentgen discovers X-ray radiation.

1899: The Bayer Company begins producing aspirin.

1900: Karl Landsteiner discovers blood groups, or types.



1905: Ernest Starling and William Bayliss isolate secretin.

1906: Frederick Gowland Hopkins discovers vitamins.

1913: John Jacob Abel builds the first kidney dialysis machine.

1913: William Henry Bragg and his son, William Lawrence Bragg, construct the first X-ray spectroscope.

1920: Earl Dickson invents the Band-Aid.

1928: Ernst Ruska develops the electron microscope.

1931: Frederick S. McKay discovers that fluoride prevents tooth decay.

1937: Daniele Bovet and Anne-marie Staub synthesize antihistamine for allergy relief.

1938: Alexander Fleming, Howard Florey, and Ernst Chain discover penicillin.

1939: George Nicholas Papanicolau develops the pap test for detecting cervical cancer.

c. 1950: The first prenatal surgery is performed.

1952: Virginia Apgar develops a scoring system to help determine the health of newborn babies.

1953: Francis Crick and James Watson discover the structure of DNA.

1955: Radial keratotomy is first performed in Japan.

1955: Johnson & Johnson introduces Tylenol.

1957: Ian Donald tests ultrasound diagnostic instrument.

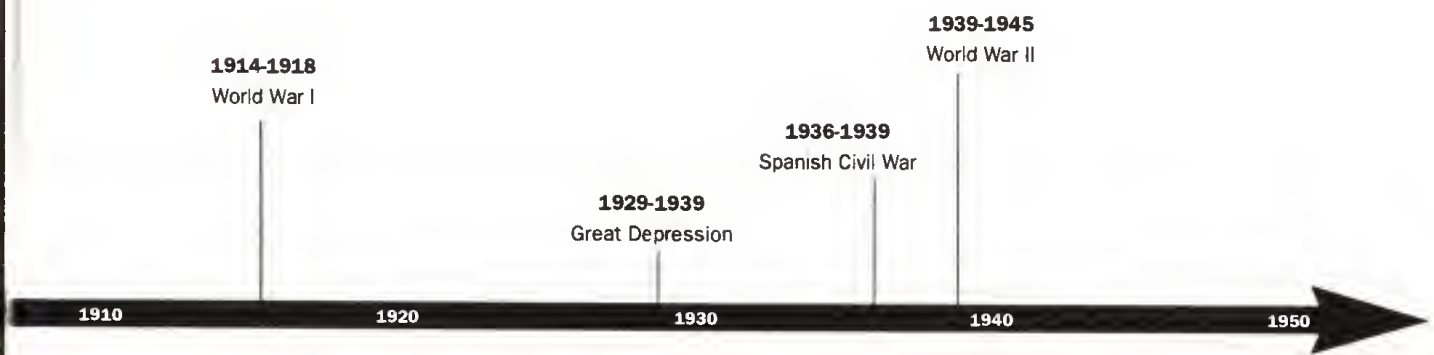
1960: Birth control pill is approved for general use.

1960: First pacemaker is implanted in a human to regulate heartbeat.

1964: Boots Laboratories begins selling ibuprofen under the brand name Brufen.

1967: Christiaan Barnard performs the first heart transplant.

c. 1967: Alan Cormack and Godfrey Hounsfield develop the computerized axial tomography (CAT) scanner.



1969: Denton Cooley implants first human artificial heart

c. 1970: Michael Phelps and Edward Hoffman develop the positron emission tomography (PET) scanner.

Early 1970s: Laser surgery techniques are perfected.

1973: Cochlear implants are used for the first time to improve hearing.

1976: The retinal scanner is developed.

1978: The first "test tube" baby is born as a result of in vitro fertilization.

c. 1981: Magnetic resonance imaging (MRI) testing is first used for diagnosing illness.

1984: Drug AZT is developed for the treatment of AIDs.

1985: Gerd Binnig, Christoph Gerber, and Calvin Quate invent the atomic force microscope.

1985: Alec Jeffreys develops genetic fingerprinting.

1986: Laparascopic techniques allow surgery to be performed with less trauma to the body.

1992: John Daugman introduces the iris scanner.

1992: Researchers announce a link between folic acid deficiency and spinal cord birth defects.

1996: Protease inhibitor drugs hailed as newest tool in AIDs treatment.

1996: RU 486 is approved by the FDA for use in the United States.

Words to Know

A

adhesive: a substance that causes one object to stick to another.

alkaloid: any of various organic compounds containing at least one nitrogen atom. Alkaloids occur mainly in many plants and some fungi. Many alkaloids, such as nicotine, cocaine, and morphine, are known for both their addictive and medicinal qualities.

amino acids: organic compounds of nitrogen and hydrogen that combine with other elements to produce proteins.

analgesic: a substance that reduces or eliminates pain.

angina: severe chest pain associated with narrowing of arteries and reduction of blood flow to the heart.

antigen: a substance that, when introduced into the body, stimulates the production of an antibody. Antigens include toxins, bacteria, foreign blood cells, and the cells of transplanted organs.

antioxidant: a substance that prevents fatty acids from combining with oxygen.

antiseptic: a substance that stops the growth of organisms that cause infection.

aspirate: to remove liquids or gases using a suction device.

B

benign: harmless; without bad intent.

blood serum: the part of the blood that does not contain blood cells. Also called plasma.

C

cardiovascular: having to do with the heart and blood circulation systems.

carotene: an orange-red substance that is changed to vitamin A in the liver.

catalyst: a substance that speeds up chemical reactions without undergoing change itself.

cauterization: use of heat to seal wounded blood vessels and prevent uncontrolled bleeding.

chlorofluorocarbons (CFCs): very stable molecules made up of chlorine, fluorine and carbon, commonly used in aerosol products and for refrigeration.

cholesterol: an organic substance found in animal tissues and various foods. Cholesterol is normally synthesized by the liver and is important as a part of cell membranes. The cholesterol level in the bloodstream can influence certain conditions, such as the development of atherosclerotic plaque and coronary artery disease.

chromosome: a threadlike strand of DNA and associated proteins in the nucleus of animal and plant cells that carries the genes that transmit hereditary information.

coenzyme: any of a group of organic compounds that usually contain a vitamin or mineral. These compounds combine with proteins to form enzymes.

collagen: a protein that makes up connective tissues such as ligaments and tendons.

congenital: something present in the body from the time of birth.

contraception: birth control.

contrast agent: dye injected into the human blood stream to detect blockages in blood flow.

cornea: the transparent covering of the eye.

coronary: of or relating to the heart and the arteries and veins which are attached to it.

D

diffraction: a change in the direction of a group of waves, such as light waves, when they strike an object or pass through a small opening.

diffusion: the continual movement of molecules in air or water.

distillation: the process of separating alcohol from the grains and fruits it was fermented from and condensing the separated alcohol into pure liquid.

dressing: materials used to cover wounds.

E

embryo: an unborn animal in the initial stages of development; an unborn human, from implantation of the fertilized egg in the uterus through the eighth week of the pregnancy.

emulsify: the suspension of one liquid inside another in which the liquids do not mix together, such as oil in water.

endocrine glands: any of a group of glands that produce hormones.

enzyme: any of numerous proteins produced by living organisms that function as catalysts, or starters, for biochemical reactions.

F

fermentation: the process of transforming sugar into alcohol.

fetus: an unborn animal in the mid-to-later stages of development; in an unborn human, the fourth to ninth month of the mother's pregnancy.

G

glucose: a monosaccharide sugar occurring widely in most plant and animal tissue. Glucose is the main circulating sugar in the blood and the major energy source of the body.

glycogen: a polysaccharide that helps with carbohydrate storage in animals. Glycogen occurs primarily in the liver and in muscle tissue.

H

hemoglobin: the iron-containing protein in the blood's red cells which carries oxygen to the cells of the body.

hemorrhage: uncontrolled bleeding.

heredity: the physical characteristics passed by the genes from one organism to another.

hypothalamus: the part of the brain that lies below the thalamus, or lower portion. Its functions are to regulate bodily temperature, certain metabolic processes, and other involuntary body activities.

I

immunosuppressant: a substance that prevents the immune system from attacking transplanted organs.

inebriation: state of the body after consuming too much alcohol.

inert: chemically inactive; a material unable to react with other chemicals.

infertility: the inability to have children.

inflammation: a localized protective reaction of tissue to irritation, injury, or infection, characterized by pain, redness, swelling, and sometimes, loss of function.

invasive: involving entry into the living body.

ion: an atom or a group of atoms that has an electric charge by gaining or losing one or more electrons.

isotope: one of two or more atoms of the same chemical element but with different masses.

L

lacerations: cuts or openings in the skin caused by injury.

leukocyte: any of the white blood cells that fight disease in the body.

ligament: a band of tough, elastic tissue that binds bones together at a joint.

ligature: the tying off of blood vessels in order to prevent uncontrolled bleeding.

lipids: a group of organic compounds, including fats, oils, waxes, sterols, and triglycerides, that are insoluble in water but soluble in common organic solvents, are oily to the touch and, together with carbohydrates and proteins, make up the principal structural material of living cells.

lymphocyte: white blood cells produced by the lymphatic tissues of the body. Lymphocytes function in the development of immunity.

M

malignant: acting with the purpose of harming.

malocclusion: a term for teeth that are crooked or misaligned.

midwife: a medically trained person, though not a doctor, who specializes in assisting with childbirth.

miscarriage: a spontaneous (unplanned) abortion of an embryo or fetus.

N

neoplasm: any of a group of cells that grow more rapidly than normal.

neurology: the study of the nervous system.

neuron: any of the impulse-conducting cells that make up the brain, spinal column, and nerves. Also called nerve cells.

nucleic acids: group of acid substances found in the nucleus of all living cells.

O

obstetrics: the medical study of childbirth.

opiate: chemicals derived from opium, a product of the poppy plant. When injected, opium gives a feeling of relaxation and happiness and relieves feelings of pain. Opiates include heroin, morphine, and methadone.

osmosis: the movement of water across a membrane (barrier) when there is a different concentration of molecules on one side of the membrane than on the other.

ovum: the egg of the human female which originates in the ovaries.

oxidant: a chemical compound that combines with other compounds to produce oxides and water.

ozone: a form of oxygen molecule with three atoms of oxygen.

P

pathology: the study of diseases.

peptide: any of various natural or synthetic compounds containing two or more amino acids linked together.

pharmaceutical: having to do with the development and distribution of drugs for medical uses.

placenta: an organ which lines the uterus and holds a fetus and its fluids during the mother's pregnancy; also contains the blood supply through which nutrition and oxygen are passed to the fetus through the umbilical cord.

plasma: that part of the blood which does not contain the blood cells. Also called blood serum.

prognosis: a prediction of the probable course and outcome of a disease.

prosthesis: an artificial limb.

puberty: the stage of adolescence when a person undergoes bodily changes, such as the onset of menstruation and the growth of facial hair.

R

retina: a light-sensitive membrane lining the inner eyeball and connected by the optic nerve to the brain.

retrovirus: a virus that invades a healthy cell and copies its DNA (genetic information) to that cell.

S

soluble: capable of being dissolved.

sputum: mucus from the lungs.

sterility: inability to have children

steroid: any of a group of fat-soluble organic compounds, including the sterols and bile acids, and adrenal and sex hormones.

sublime: to pass directly from a solid to a vapor, skipping the liquid state.

sutures: surgical stitches to hold the edges of a wound together.

synthetic: substances produced by human attempts to blend or combine materials that do not naturally occur together.

systemic: acting throughout an entire system. Systemic medications affect the whole body, not just a small part.

T

tachycardia: a fast, irregular heartbeat.

T-cell: white blood cells that attack disease-causing organisms or other foreign bodies, such as transplanted organs, in the body.

therapeutic: something used for treatment of illness.

thrombolysis: process of dissolving blood clots.

toxin: an invading organism that will cause disease and damage the body.

toxoid: a disease-causing organism that is chemically treated to end its ability to cause disease. Treated toxoids help generate immunity.

tubal ligation: the tying of ovarian tubes in the female to prevent the release of ova (eggs) and provide permanent birth control.

U

ultrasound: frequencies above the range of human hearing; in medicine, the use of ultrasonic waves to create pictures of internal body structures and organs.

V

vas deferens: the tubes that connect the male testicles to the penis.

vasectomy: the cutting and tying of testicular tubes in the male to prevent sperm from causing a pregnancy.

ventricular fibrillation: irregular contractions of the heart.

volatility: ability of a liquid to change to a gas at room temperature.

Z

zygote: a fertilized ovum or egg.

Abbe, Ernst

German researcher Ernst Abbe (1840-1905) is considered one of the first optical engineers (people who create instruments that enhance sight). Abbe's work designing microscopes and lens systems set new standards for the development of scientific optical instruments. Among Abbe's inventions were lenses that corrected blurring and color aberrations (irregularities).

Ernst Abbe's work designing microscopes and lens systems set new standards for the development of scientific optical instruments.

Abbe is best known for his collaboration with **Carl Zeiss** (1816-1888). Zeiss owned Zeiss Optical Works, a company in Jena, Germany, that manufactured specialized optical instruments. In 1855 Zeiss decided that Zeiss Optical Works should concentrate on building precision tools for the growing research market. Few people at the company, however, had the design knowledge to produce such instruments. Knowing that he would have to get help from outside sources, Zeiss hired Abbe as a consultant.

At the time Zeiss approached him, Abbe was working as an untenured university lecturer. While recognized as being intelligent and industrious, Abbe had been unable to secure a professorial position. Zeiss's offer was very appealing, because it allowed Abbe to make use of his mathematical skills. For the next few years Abbe worked on new lens grinding procedures with Zeiss Optical Works glassmaker Otto Schott, research that resulted in near-flawless lenses. Abbe's work at Zeiss brought him fame and respect in the scientific community. In 1875 he was offered a professorship at Jena University, which he accepted. Abbe was later offered a position at the more prestigious University of Berlin, but he declined the job on order to continue working at Zeiss Optical.

In 1876 Zeiss made Abbe a partner in his company. When Zeiss died in 1888, Abbe took over the day-to-day operations of Zeiss Optical Works. For the rest of his career, Abbe both ran the company and established the Carl Zeiss Foundation, an organization for the advancement of science and social improvement.

[*See also* **Microscope, compound**]

Abortion

An abortion (an event or procedure that terminates or brings a pregnancy to an end) can be spontaneous (unplanned) or induced (planned). The spontaneous abortion of a fetus (name given to unborn young from the end of the eighth week of development to the moment of birth) is called a miscarriage, and occurs in about twenty-four percent of all pregnancies. In the case of miscarriage, there is usually some problem with the fetus, or with the ability of the woman's uterus to support the fetus's development. The most common cause of miscarriage is a low level of prenatal hormones. A planned abortion occurs when, for personal or medical reasons, the embryo (name given to unborn young up to the beginning of the eighth week of development) or fetus is removed before gestation (the carrying or development of young in the uterus from conception to birth) is complete. Planned abortions are considered medical procedures and are usually performed in a hospital, clinic, or doctor's office under the supervision of trained staff.

Most miscarriages and planned abortions occur during the first trimester (months one through three) of a woman's pregnancy, when the embryo is just beginning to develop. A much smaller number of abortions and miscarriages occur in the second trimester (months four through six), when the fetus has developed further. Abortions are rarely performed in the third trimester (months seven through nine), because the fetus may be viable (able to survive outside the uterus) with intensive hospital care. Viability generally occurs at the twenty-fourth week of pregnancy when the fetus weighs at least 21 ounces.

Procedures

Procedures for conducting a planned abortion vary according to the trimester of the pregnancy. In the first trimester, uterine aspiration (the suctioning and cutting of fetal material from the womb) under local anesthe-

Legal and Moral Issues

There is great debate in the United States about legalized abortion. In its 1973 *Roe vs. Wade* decision, the United States Supreme Court held that a woman has the right to end a pregnancy for any reason during the first trimester. States may regulate the use of abortions during the second trimester as long as the woman's health is not threatened. During the third trimester, individual states may forbid abortion unless the life or health of the mother is threatened.

The abortion issue has such emotional power that it has influenced political elections and led to protests against clinics, offices, and hospitals where abortions are performed. Pro-life advocates view abortion as the killing an unborn child, while pro-choice supporters believe that women should be free to make their own decisions about pregnancy termination. Recent developments concerning abortion—such as President Bill Clinton's 1996 veto of a bill that would have overturned rarely performed partial birth abortions—have only added fuel to the debate.

sia is most common. Aspiration is also used to remove any lingering tissues from a miscarriage.

A recent and more controversial first trimester abortion method is **RU 486**. Known as the "abortion pill," RU 486 was created by French biochemist Etienne-Emile Baulieu (1926-; cofounder of the International Society for Research in Biology and Reproduction) and introduced in France in 1988. RU 486 works by changing the hormonal environment of the uterus so that it interferes with the development of the fertilized egg. Once this interference occurs, the fertilized egg and lining separate from the uterine wall and are expelled through bleeding.

For pregnancies that occur in the second trimester, two other methods are utilized. In the first method, a saline (salt water) solution is injected into the uterus, which kills the fetus. The woman then has induced (brought on) labor, which expels the fetal tissue. The second—and more common—method is to inject prostaglandins (hormone-like substances) into the uterus to kill the fetus, followed by the induction of labor and expulsion of fetal material.

Complications from a properly performed abortion are rare, but illegal abortions done by nonprofessionals or attempted by the woman herself

can cause many problems, including infection, uncontrolled hemorrhaging (bleeding), and can even result in death.

[*See also* **Hormone**]

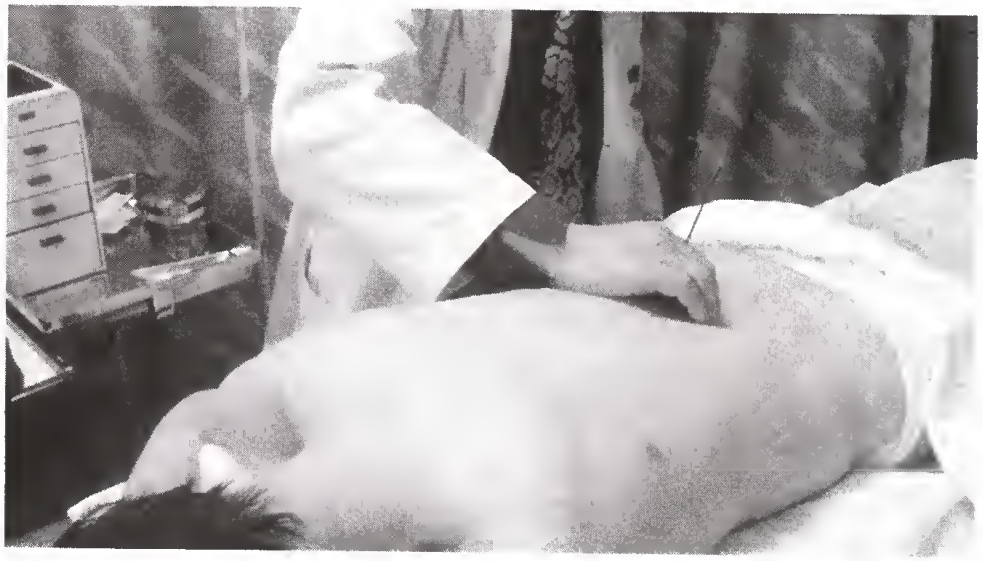
Acupuncture

Acupuncture is an ancient method for relieving pain and treating disease using very fine metal needles. While the invention date of acupuncture is not known, the theory behind it has been handed down through the centuries. According to acupuncture practitioners, certain points on the surface of the body are linked to internal organs. When a patient becomes ill, the illness often manifests itself on a surface site. Treating the external site—or a specific area of skin—creates a link to the internal imbalance.

Philosophy Explains Illness

Early Chinese medical practitioners learned that certain areas of the skin showed sensitivity during illness or organ malfunction. These points of sensitivity were discovered to be part of a pattern. Chinese doctors drew "body maps" to help keep track of the various points. The lines they used to connect the pattern points were called meridians. Each meridian was linked to certain body organs and physical conditions.

According to Chinese Taoist philosophy (a system of religion based on the teachings of philosopher Lao-tse), these points of skin sensitivity relate to the life force or energy called *Qi*, which circulates throughout the



A doctor uses acupuncture to treat a patient.

body. Balance within the body depends on the interplay between two forms of energy, called *yin* and *yang*. When these forces are in harmony, the body is healthy. When either force becomes dominant, disease or pain occurs. Acupuncture restores the balance between yin and yang by tapping into the body's channels, or meridians, through which these energy forms flow.

The basic reference book on acupuncture is the *Nei Ching,* or *Yellow Emperor's Classic of Internal Medicine,* said to have been written by Huang Ti (2697-2596 B.C.), also known as the Yellow Emperor. The *Nei Ching,* or "Canon of Internal Medicine," is divided into two parts. The first, *Su Wen,* explains the theoretical basis of Chinese medicine. The second, *Ling Shu,* tells exactly how to use acupuncture to treat and prevent every then-known disease and gives detailed needle insertion points. An edition of the original *Nei Ching* was compiled by Wang Ping in A.D. 762 and revised around A.D. 1200. This later edition is the basis for the modern *Nei Ching,* which remains the foundation of today's acupuncture.

Early Acupuncture Tools

The earliest acupuncture needles are thought to have been made of stone, fish bones, and bamboo. These materials were later replaced by metals such as copper, brass, silver, and gold. Today most acupuncture needles are made of stainless steel, gold, or silver. The needles may be several inches long and are inserted to various depths and then twirled or vibrated. A tiny electric charge may be added. Insertion is painless or, at the most, mildly uncomfortable for a moment. Acupuncture students practice needle insertion on themselves thousands of times while perfecting their technique. The *Nei Ching* prescribed 365 insertion points; modern acupuncturists use 650 to 800.

The earliest acupuncture needles were thought to be made of stone, fish bones, and bamboo.

Westerners Experiment with Acupuncture

Knowledge of acupuncture was brought to the West by Jesuit missionaries in the 1600s, although detailed descriptions of acupuncture theory and practice were not available to Westerners until Soulié de Morant's writings in the 1940s. Western interest in acupuncture, as well as the medical philosophies that accompany its practice, has been growing steadily since then.

Today, acupuncture is still an important element of Chinese medicine. In fact, acupuncture is often used as an anesthetic when major surgery is performed in China. Western scientists acknowledge acupuncture's effectiveness, noting that the skin does in fact have different levels of electrical resistance at the ancient acupuncture points. Western researchers spec-

ulate that acupuncture may stimulate production of the body's natural pain relievers, or endorphins, or it may interrupt nervous system pain messages.

[*See also* **Anesthesia; Endorphin and enkephalin; Surgical instruments**]

Adhesives and adhesive tape

Adhesives are substances that hold the surfaces of materials together, often permanently. Natural adhesives (of plant or animal origin), synthetic (artificially produced) adhesives, and combinations of the two can be categorized according to whether they are activated by heat and whether they form rigid or stretchy bonds.

Adhesives were first used medically in bandages invented by the German pharmacist Paul Beiersdorf in 1882. Epoxy resins (fibers softened by heating) were developed in the 1950s. These resins permitted the bonding of materials such as glass and metal that earlier adhesives failed to hold together. Superglue is a modern example of very strong adhesive that sets in seconds and works on many different materials. Users sometimes find that this liquid adhesive works too well, since it can cause skin to stick together.

Used to Repair Cuts

Adhesives are being investigated as replacements for sutures and surgical staples.

Widely used in everyday applications, adhesives are rapidly finding their way into medicine. Adhesives are used as replacements for sutures (stitches) and surgical staples. One tissue adhesive, *Histoacryl Blue* (also known as "HAB"), is used in Canada to repair small wounds, but not moist cuts or parts of the body that move. HAB has impressed doctors in one American study because children's lacerations (cuts) could be repaired more quickly than wounds could be sutured (17 minutes to suture a wound versus 7 minutes to glue it with HAB). Another plus is that the adhesive peels off by itself in several days, so the repair does not require the patient to return to the doctor's office to get sutures removed.

Superglues are also being used experimentally for eye surgery. Adhesives in the medical setting may be especially valuable in microsurgeries (operations done under a microscope or other magnifying lenses). Two natural-based adhesives, one made from blood-clotting compounds and another from mussels, are currently being tested in Europe and the United States.

Adrenocorticotropic hormone (ACTH)

Adrenocorticotropic hormone (also known as "ACTH") is a pituitary hormone. A hormone is a chemical produced by a gland. The pituitary gland, located below the brain, secretes (releases) several hormones that control other glands which regulate growth and metabolism. ACTH's principal function is to stimulate the cortex (outer layer) of the adrenal glands (located near the kidneys) to secrete a group of steroid hormones called glucocorticoids. Glucocorticoid hormones control the body's use of sugar and also help regulate biological functions during stressful moments.

The properties of ACTH were first investigated in the 1930s. In 1933 research groups headed by Canadian biochemist James Collip, American biologist Herbert Evans (1881-1971), and Argentine physiologist Bernardo Houssay (1887-1971) used pituitary extracts to stimulate the adrenal cortex (the center of the adrenal glands). American biochemist Choh Hao Li was one of several scientists who isolated ACTH in 1943 and synthesized it in 1963.

Today, ACTH is often prescribed to reduce inflammation (tenderness and swelling caused by infection, injury, or illness) and relieve pain. This use of ACTH was first studied by American medical researchers Philip Hench (1896-1965) and Edward Kendall (1886-1972), who were looking for an effective treatment for arthritis. During World War II (1939-1945) Hench headed the first program to mass-produce ACTH for medical use. In 1948 and 1949 Hench and another colleague were the first researchers to use ACTH successfully in arthritic patients. Hench and Kendall received the 1950 Nobel Prize in physiology or medicine for their achievement.

ACTH is often used to treat rheumatoid arthritis, colitis, and some types of hepatitis.

ACTH is commonly used to reduce inflammation in rheumatoid arthritis (a disabling inflammation of joints and tissues), ulcerative colitis (an inflammatory bowel disease), and some types of hepatitis (an inflammatory disorder of the liver).

Aerosol spray

An aerosol is a gaseous suspension (hanging) into air of solid or liquid particles. The word "aerosol" also refers to the dispenser or package used to change the ingredient inside the container into an aerosol. The aerosol spray can dates back to 1926, when Norwegian inventor Eric Rotheim discovered that a product could be sprayed from an aluminum can that had

been injected with gas or liquid to build pressure. In recent years, the basic metal aerosol can has been joined by plastic and glass containers.

In 1939 American Julian S. Kahn received a patent for a disposable spray can, but the product remained largely undeveloped. Lyle David Goodhue, credited as the inventor of the spray can, earned a patent for a refillable aerosol spray can in 1941. In 1949 Bronx machine shop proprietor Robert H. Abplanalp developed a cheap, efficient valve, which helped spray cans to come into widespread use.

Inside the aerosol spray can is a main ingredient, such as an asthma medication, and a propellant (something that provides thrust or movement). Early propellants were liquified gases such as hydrocarbons, carbon dioxide, or nitrous oxide. The combined ingredients are pressure-sealed, then released by pressing the valve. The propellant Freon became very popular because it is chemically inert (inactive), nonflammable, and nontoxic (nonpoisonous).

Aerosol spray is an efficient way to dispense drugs that need to be inhaled in measured doses. For this reason medications for asthma, allergies, and lung conditions such as cystic fibrosis are commonly packaged in aerosol cans.

CFCs Blamed for Ozone Layer Depletion

Chlorofluorocarbons (CFCs), including Freon, were used extensively as aerosol propellants. Beginning in the 1970s scientists noticed a massive decrease in the amount of ozone present in the ozone layer, part of the upper atmosphere around the earth that shields the earth from harmful solar radiation. Ozone levels had been constant throughout geological time, but over Antarctica the levels had dropped so low that there appeared to be a "hole" in the ozone layer. As the ozone hole grew larger, scientists began to suspect that CFCs were responsible. CFCs react with chlorine and break down, thereby destroying the ozone layer and allowing more radiation from the sun than is normal to reach the earth.

Aerosol products have many uses, from hair care to cleaning and disinfecting.

In 1978 the U. S. Government banned the use of certain CFCs, and manufacturers of aerosol products had to find other propellants. Some of the alternative propellants include hydrochlorofluorocarbons (HCFCs), hydrofluo-

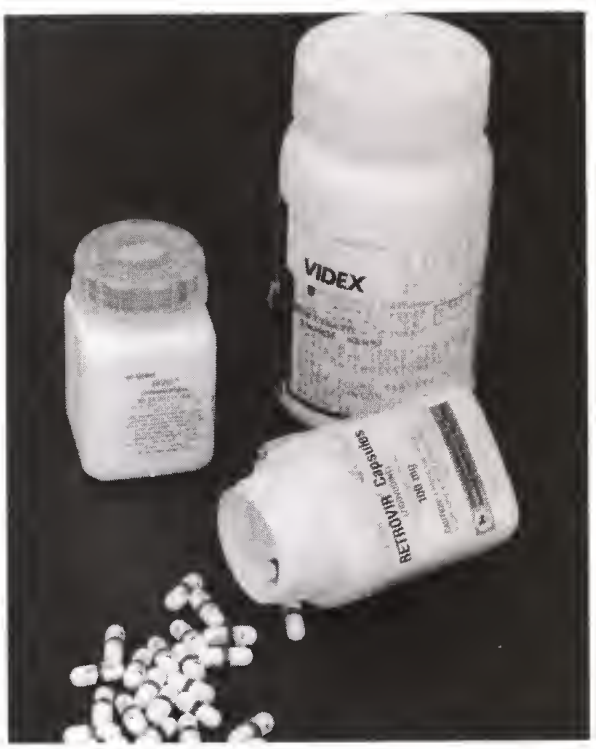
rocarbons (HFCs), and carbon dioxide. In 1987 an international treaty known as the Montreal Protocol on Substances that Deplete the Ozone Layer decreed that CFC use should be decreased. Two years later 93 nations agreed to stop producing CFCs entirely and help poorer nations make the transition to other chemistries.

Now less than two percent of American-made aerosol cans contain CFCs. Those that do contain CFCs mostly dispense drugs, such as asthma inhalers. The other chemical compounds that have been developed to replace CFCs thus far are more expensive and less versatile. One promising alternative propellant is Polygas, developed by Scottish inventor Bernard D. Frutin. This mixture of carbon dioxide and acetone is reportedly superior to other propellants because it is more environmentally sound, less flammable, and creates higher and more consistent pressure.

[*See also* **Nitrous oxide**]

AIDS therapies and vaccines

Public awareness and understanding of Acquired Immune Deficiency Syndrome (AIDS) and Human Immune Deficiency Virus (HIV) has increased since the first AIDS cases were diagnosed in the 1980s. There are several reasons for this expanded understanding. The development of promising therapies and vaccines has given hope to infected individuals, while education—from public service announcements to classroom discussions—has helped decrease the spread of AIDS in certain populations.



Three of the drugs commonly used to treat AIDS are DDC (left), DDI (right), and AZT (front).

Treating the Virus

There are several reasons why AIDS is difficult to treat. HIV is a retrovirus (a virus made up of ribonucleic acids, or RNA, instead of deoxyribonucleic acids, or DNA). All retroviruses use a special enzyme, called reverse transcriptase, to copy their genetic material directly into a host cell. HIV is lytic, meaning that it kills the cells it invades. The virus can then become inactive for long periods of time. Researchers are trying to learn how and why the virus reactivates.

What Is AIDS?

AIDS is a progressive disease with many symptoms. These symptoms, which can take years to develop, include severe weight loss, bleeding, pneumonia, and skin lesions (sores). Many AIDS patients are infected by *Pneumocystis carinii* (PCP), a condition usually found in people whose immune systems are not functioning properly, and *Kaposi's sarcoma*, a malignant condition characterized by pink or purple flat or raised blotches appearing under the skin. In October, 1992, the Centers for Disease Control proposed a new definition of AIDS that included three new illnesses, including invasive cancer of the cervix, bacterial pneumonia, and pulmonary tuberculosis.

Treatment must either kill the virus or stop it from multiplying. The ideal treatment would kill the virus without harming the HIV host cells. Developing such an antiviral drug is extremely difficult, because viruses use a cell's own genetic machinery to reproduce. This makes it hard for scientists to distinguish between viral and host cell protein molecules.

In 1984 scientists began testing more than 300 drugs to learn their effectiveness against HIV. The researchers knew that a good drug had to be able to interrupt the virus life cycle at any one of several stages. A drug called azidothymidine (AZT) showed special promise. AZT does not cure or prevent AIDS, but it can slow down the progress of the disease, especially when used with other treatments. AZT works by preventing reverse transcriptase from reproducing HIV in the host cell's DNA. In 1993 the effectiveness of AZT was examined in a joint French and British study. The study questioned the practice of giving AZT to patients who have the HIV virus, but exhibit no symptoms.

There are currently many therapies at different phases of development and testing. Some antiviral substances, including interferons, have been effective in preventing the virus from budding. Fewer buds mean less virus to infect other cells. The drugs Dextran sulfate and soluble CD4 stop the virus from attaching to the host cell. Other drugs interfere with viral replication.

Developing Vaccines

Therapies are used by people already infected with the virus. A cure or vaccine to prevent the disease, though, is the ultimate goal. Vaccina-

tion is the simplest, safest, and most effective way to prevent infectious disease.

Researchers have yet to develop an effective vaccine against HIV for several reasons. The ability of the virus to hide in host cells makes it difficult for the body's antibodies (disease fighting cells) to find the virus and attack it. The HIV virus also mutates or changes its genetic composition very rapidly. To understand how hard it is to produce a vaccine against HIV, consider the rhinovirus. This virus, which causes the common cold, also mutates rapidly. Because of this mutation, no vaccine exists to prevent colds.

Because HIV is a fatal infection, the need for effective treatments is imperative. Scientists from various countries are working together to develop a vaccine to prevent the transmission of HIV. This cooperation makes it much more likely that researchers will succeed in producing a vaccine against HIV.

[*See also* **Enzyme; Interferon**]

The ability of HIV to hide in host cells makes it difficult for antibodies to fight the virus.

Alcohol, distilled

Alcohol is perhaps the oldest drug used by humans. Alcohol affects the body according to its level of concentration in the blood, producing a feeling of well-being at the smallest blood alcohol concentration, to unsteadiness when walking, slurring of the speech, drowsiness, then inebriation (a drunken state) at higher levels. Long-term use of alcohol can cause severe

Wine is processed in a modern distillery.

internal damage to the human body. As a result, alcohol is no longer regarded as a medicine.

How Distilled Alcohol Is Produced

Distilled alcohol, also called "spirits," contains 40 percent to 50 percent alcohol because the distillation process concentrates the alcohol by removing the water. To make distilled alcohol, a mash of grains or fruit juices is prepared and fermented. The mash is heated in a boiler, causing the alcohol to boil away. The alcohol vapors are collected, then cooled in a condenser.

The Romans called distilled alcohol "aqua vita" or "water of life."

The Romans are credited with discovering how to distill alcohol. They called the final product "aqua vita" or "water of life." Distillation for medicinal purposes probably began in the early twelfth century in Italy, when wine was distilled to produce brandy. Distilled alcohol has been used as an **anesthetic** (a drug or preparation that produces unconsciousness or increased insensitivity to pain) and as a wound cleaner and antiseptic (a substance that cleans and sterilizes by stopping the growth of microorganisms on body tissues and surfaces). Distilled alcohol's purity makes it a good preservative, and it is still used in liquid medications.

Alcohol Use Loses Favor

Distilled alcohol's use as an anesthetic is based on the effects it has on the brain, including relaxation and insensitivity to pain. Because the anesthetizing effects of alcohol are less predictable than the drugs available to modern-day anesthetists, alcohol is no longer used professionally to anesthetize patients.

Other former medical uses include adding distilled alcohol to intravenous solutions (IVs) to provide calories to patients, a practice that has been stopped as doctors have learned more about the toxic effects of alcohol on the human body.

Distilled alcohol exists in an undrinkable form called industrial alcohol, which is used in the manufacture of thousands of goods. Most industrial alcohol is now made synthetically from natural gas or petroleum gases. This class of alcohol includes isopropanol (rubbing alcohol), used to clean wounds and skin and to cool the skin.

Ambulance

The origin of the ambulance was tied to the needs of war. Battlefields were often miles from medical tents. An injured soldier could die on his to treat-

ment if he had to be carried by men on foot. Although we may think of ambulances in terms of automobiles, earlier forms of ambulances were used as long ago as the middle ages, when men wounded in battle during the Crusades (a series of eight extended battles fought by European noblemen from 1095-1291 to protect the Christian Byzantine empire from Muslim Turks) were transported by horse-drawn wagons to centralized treatment centers.

Father of the Modern Ambulance

The modern ambulance—at least the horse-driven version—was created by Frenchman **Dominique-Jean Larrey** (1766-1842) in 1792. Larrey, Napoleon's private surgeon, wanted to improve battlefield treatment of wounded soldiers. He designed a horse-drawn "flying ambulance" to carry surgeons and medical supplies onto the field of battle during the Rhine campaign of 1792.

For the Italian campaign of 1794, Larrey used light ambulance carriages with stretchers to carry the wounded. In Egypt in 1799, local camels powered Larrey's ambulances. With fellow surgeon Pierre Percy (1754-1825), Larrey formed a battalion of ambulance soldiers, including stretcher bearers and surgeons. Larrey's ambulances and the swift medical attention they brought significantly boosted the morale of Napoleon's troops.

Ambulance service was expanded from the military to the civilian world in 1869 by Bellevue Hospital in New York City. The Larrey "flying ambulance" remained standard until the first motorized ambulances appeared around the turn of the century. These motorized vehicles were pioneered by the Panhard-Levassor partnership of France.

A modern ambulance speeds off in response to an emergency call.

Air and Ground Ambulances

The first airborne ambulances were hot-air balloons used to evacuate wounded personnel from Paris during a Prussian siege in 1870. Helicopters began to transport wounded soldiers during World War II (1939-1945) and became vital evacuation vehicles in the Korean (1950-1953) and Vietnam (1965-1973) wars. Today, air ambulances—both fixed-wing and helicopters—are increasingly used for quick transportation of patients, particularly in busy cities, but also in rural areas where medical care may be a great distance from the scene of an accident.

Until the mid-1960s, ambulances were mostly modified hearses, since these vehicles could transport patients in a supine (lying down on one's back) position. Since hearses were designed to carry corpses instead of living patients needing care, they had little room for supplies or attendants, let alone treatment en route to the hospital. A National Academy of Science/National Research Council report in 1966 focused attention on the need for both professional training of emergency medical technicians (EMTs) and improvements in ambulance design. This report resulted in today's modern van ambulance, with it's working space and sophisticated supplies and equipment. The van ambulance is operated by medical paraprofessionals, so that the ambulance is no longer simply a transportation vehicle—it is also a moving treatment center.

Amniocentesis

Amniocentesis is the process of removing a sample of amniotic fluid from the mother's uterus (a pear-shaped organ located in the pelvis where unborn young develop) in which the fetus (growing baby) floats. The fluid and fetal cells in the fluid are then analyzed to check for and diagnose possible genetic disorders.

The Bevis Study

Until amniocentesis became available, **prenatal (prebirth) diagnostic techniques** were severely limited and risky. By the late 1920s or early 1930s, using a needle to obtain samples of amniotic fluid was an accepted—if rarely used—technique. It was only after a British doctor published the results of his study in the February, 1952 issue of *Lancet* that the use of amniocentesis became widespread. Douglas Bevis, the doctor who conducted the study at St. Mary's Hospital in Manchester, England,

Other Prenatal Diagnostic Tools

Amniocentesis is one of the most common prenatal diagnostic tools. While the development of this procedure marked an important advance, amniocentesis is just one tool doctors use to determine fetal status. Other prenatal diagnostic techniques include **ultrasound** scanning (the use of sound waves to produce a picture of the developing fetus), and fetal blood sampling (in which a fetalscope is inserted surgically through the uterine wall to collect a clear blood sample). Nuclear Magnetic Resonance Imaging (NMR) reveals biochemical information about fetal tissues and organ structure, while DNA testing, introduced in 1976, is used to identify specific gene disorders.

chemically analyzed the iron and urobilinogen content of amniotic fluid to determine the possibility of hemolytic (blood) disease in unborn children. The doctor used amniocentesis to determine fetal risk if an Rh-negative woman was impregnated (made pregnant) by an Rh-positive man. Bevis's study of amniocentesis is considered a landmark event in promoting the procedure. His technique was later refined by another researcher who measured amounts of bilirubin (a reddish-yellow organic compound made from homoglobin) in the amniotic fluid of Rh-sensitized women. These test results were published in 1961.

Using Amniocentesis as a Diagnostic Tool

Amniocentesis eventually enabled doctors to predict fetal sex. This ability was based on the 1949 observations of doctors Murray Barr and Ewart Bartram, who noted that all female cells, but no male cells, contain a chromatin mass (made of nucleic acid and protein) on the edge of the nucleus (a complex body within a cell that contains the cell's hereditary material and controls its growth). If the fetal cells found in the amniotic fluid contain this mass (known as a "Barr Body"), then the fetus is female. Knowing the sex of the fetus is important in assessing the risk of a child being born with a sex-linked (affecting one sex only) disease such as hemophilia.

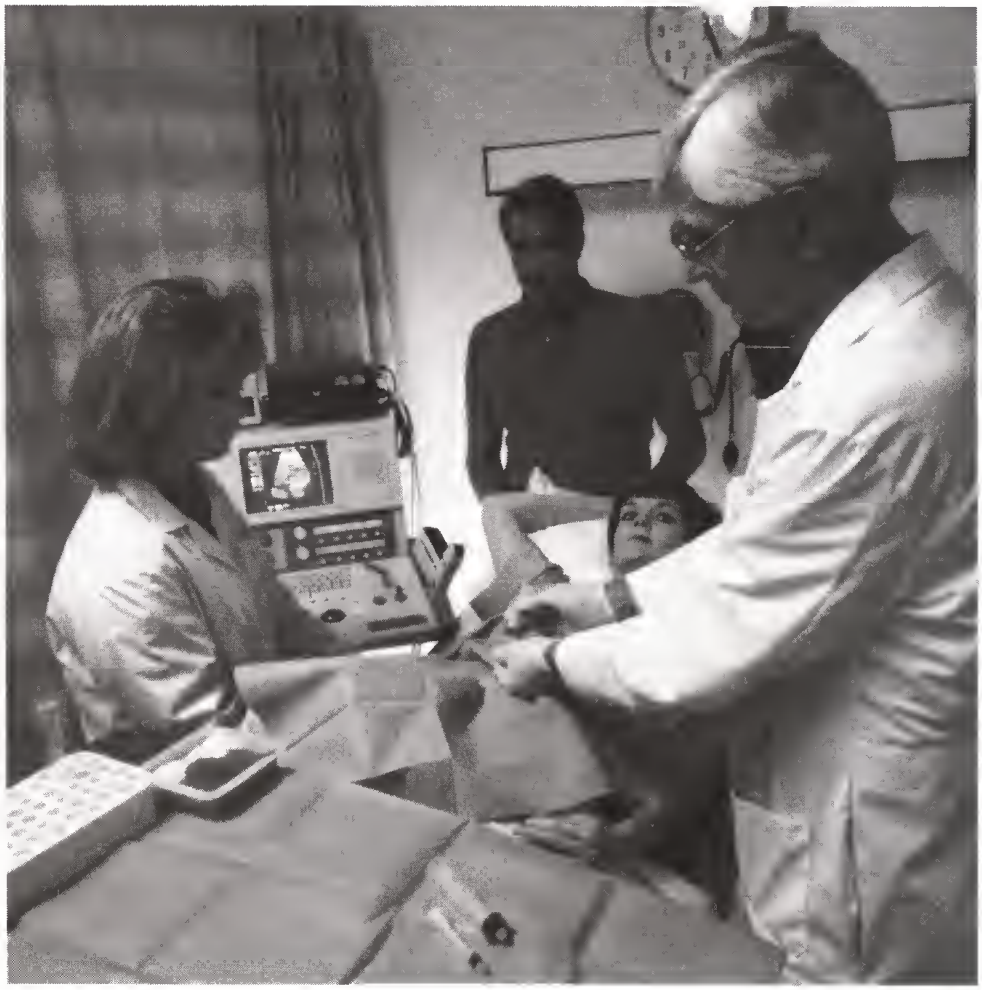
There are now over 500 hereditary diseases that can be diagnosed through amniocentesis.

During the mid-1960s it became possible to grow human cells in the laboratory and perform chromosomal testing. Chromosomes (the hereditary material found in the cell's nucleus) carry genes, which contain the chemical instructions for inherited characteristics. Chromosomal testing made it possible to determine whether a fetus was affected by Down's syndrome, which causes severe mental retardation as well as physical and

developmental deficiencies. The first such diagnosis was made in 1968 by Dr. Carlo Valenti in New York. Testing the fetus for genetic disease is now widely practiced, particularly for pregnant women over the age of 35 (who are at greater risk of conceiving a child with Down's syndrome) and parents with a family history of genetic problems. There are now over 500 hereditary (family) diseases that can be diagnosed through amniocentesis and other diagnostic techniques.

How Amniocentesis Is Performed

During amniocentesis, a doctor inserts a fine needle into the amniotic sack inside the uterus. A sample of the amniotic fluid is drawn out and cultured (grown) in the laboratory. In the early days of the procedure, doctors guided the needle into the uterus by touch and tried to be careful not to prick the placenta (sack), the fetus (baby), or the umbilical cord. Since the 1980s ultrasound devices have decreased the risk of damage during the



A doctor and nurse perform amniocentesis on a patient. The procedure is used to learn about the health of unborn babies.

procedure by providing a visual image of the fetus inside the uterus, which allows the doctor to guide the needle while watching the device's monitor.

The amniotic sample is taken from the fifteenth to the eighteenth weeks of the pregnancy (40 weeks is considered the normal length of a human pregnancy). Before the fifteenth week the amount of amniotic fluid present is insufficient to allow sampling. Culture and analysis of the specimen takes 10 to 21 days, which means that diagnosis of any fetal problems is not available until the twentieth or twenty-first week (fifth month) of the pregnancy. **Chorionic villus sampling** (CVS), an alternative method of fetal diagnosis, can be done much earlier in the pregnancy, but CVS carries a higher risk of causing spontaneous **abortion** (miscarriage). Amniocentesis, which causes miscarriage at a rate of 0.5 percent to 1 percent, is now being tried earlier in the pregnancy than 15 weeks.

The rise of amniocentesis as a tool for accurate prenatal diagnosis has made it possible to treat some medical problems before birth while the baby is in the uterus. In cases where treatment is not available, parents have faced the difficult option of giving birth to a child with life-threatening conditions or terminating the pregnancy (by abortion). Amniocentesis can also reveal how developed a fetus is. This knowledge is especially important when early delivery may be necessary. For example, when amniocentesis shows that the fetal lungs are not mature enough to work properly after birth, a hormone can be injected into the fetus to help the lungs develop.

[*See also* **Rh factor**]

Amputation

Amputation is the surgical removal of all or part of an appendage (such as a leg or arm). Amputation has been practiced since earliest times, but usually out of desperation, as in the case of a crushed limb. Early attempts at amputation were often unsuccessful because the patient was likely to die from bleeding or infection during or soon after the procedure was performed.

Early attempts at amputation were often unsuccessful because the patient was likely to die from bleeding or infection.

From the time of ancient Greek physician **Hippocrates** (460-370 B.C.) until the 1500s, amputations usually involved cutting through dead rather than living tissue because dead tissue did not hemorrhage (bleed uncontrollably). Stumps, or the remaining limb tissues, were then sealed with red-hot irons or boiling oil or tar. This burning procedure stopped most bleeding and was also thought to help prevent gangrene (tissue rot-

ting). In the mid-1500s, German surgeon Fabricius Hildanus (1560-1634) began using a red-hot knife for amputations, which both removed the limb and controlled bleeding at the same time.

Paré's Discovery

The post-amputation sealing process was called cauterization. Cauterization was terribly painful for patients, who usually did not have any anesthesia during the procedure. French surgeon **Ambroise Paré** (1510-1590) helped change this painful fact in the 1500s. By Paré's time, gunpowder had made battlefield injuries so horrible that amputation became commonplace. Even amputation at the thigh, which previously had been very rare because of the extremely heavy (usually fatal) bleeding, was now often necessary. Paré's great improvement was ligature (tying off of the blood vessels rather than cauterizing them). Earlier surgeons had proposed ligature, but it was Paré who developed a successful technique to carry it

Scientific advances in the development of prosthetic devices have given amputees greater mobility.

out. He also devised a curved instrument he called a crow's beak to draw out the severed blood vessels.

Petit Designs the Tourniquet

Although Paré's method was more effective than cauterization, it did not always work because of the large number of blood vessels involved in major amputations. A way was needed to control bleeding until the surgeon could tie off all the vessels. This control was finally provided by the effective tourniquet (pronounced "turn-i-ket") designed by J. L. Petit (1647-1750) in 1718. Petit's screw tourniquet was fixed to the lower abdomen and put direct pressure on the main artery.

With bleeding controlled by Petit's tourniquet, Paré's ligatures were now practical. Amputations on the battlefield were carried out swiftly and in great number. One French surgeon performed 200 amputations in a single day during the Battle of Borodino (Russia) in 1812. Unfortunately, while patients no longer died routinely of bleeding during an amputation, many died of infections afterward. It remained for **Joseph Lister** (1811-1886) to introduce **antiseptics** for amputation to become a successful procedure. As modern physicians learned new, effective ways to treat illnesses and infections, amputation steadily became less necessary.

Today, the majority of patients who undergo amputations do so for medical reasons (such as diabetic complications). With the problems of bleeding, anesthesia, and infections solved, the emphasis is on construction of effective prosthetics (**artificial limbs**) and physical therapy that allow patients to return to a fairly normal life.

[*See also* **Artificial limbs and joints; Surgical instruments**]

Anaphylaxis

Anaphylaxis is a violent allergic reaction of the whole body which can result in death. During anaphylaxis, the allergic person's throat swells so much that she or he cannot breath, while internal organs may start to shutdown. The immune system's attempt to rid the body of a particular substance actually turns against the body itself.

When research on the immune system was progressing in the 1800s, most scientists thought that the body's reactions to invaders were always protective. While researching experimental smallpox innoculations in

1798, **Edward Jenner** (1749-1823) observed that patients given a second shot often suffered violent reactions. Despite this risk, people were more afraid of the disease than possible inoculation side effects. Jenner's experimentation, which included inoculating subjects with both cowpox and smallpox, eventually led to the development of a successful—and safe—smallpox vaccine.

The first complete study and description of negative immune responses was produced by two Frenchmen, physiologist Charles Richet and physician Paul Portier (1866-1962). During a scientific cruise on the yacht of Prince Albert of Monaco (a small principality on the Mediterranean Sea), Albert suggested that Portier and Richet study the poison (toxin) produced by the tentacles of the Portuguese man-of-war, a jellyfish. Back in France, the two men continued their studies with extracts of toxin from a sea anemone (a flower-like marine creature). While looking for a toxic dose level, they injected dogs with sea anemone venom. Dogs that survived were given time to recover and then reinjected. Richet expected that the first exposure to the toxin would create a certain amount of immunity in the dogs, the same way that getting a virus gives someone immunity to another encounter with the same disease. Instead, the initial exposure made the dogs hypersensitive. A second, much smaller dose of toxin quickly killed them. Since this result was the opposite of a protective immune response, or *prophylaxis,* Richet named the hypersensitive reaction anaphylaxis. Richet's identification of anaphylaxis won him the 1913 Nobel Prize for medicine.

After further research, it was discovered that many substances people are allergic to, particularly foods and toxins from animals (such as bee venom), can cause strong reactions. This knowledge provided a valuable warning to physicians engaged in serum (anti-poison) therapy. The researchers began checking patients for possible sensitization before injecting potentially toxic amounts of serum. Those patients with an initially severe reaction to an allergen (or allergy-causing agent) were advised to carry **epinephrine** (an artificial hormone) to inject immediately if they had a severe reaction.

[*See also* **Hormone**]

Anesthetics

Anesthetics are substances administered to deaden pain or produce a state of anesthesia (a condition in which some or all of the senses, especially

touch, stop functioning or are reduced). Early Chinese practitioners used **acupuncture** (the insertion of thin, solid needles into specific locations on the body) and the smoke of Indian hemp (a tough fiber obtained from the stems of a tall plant) to dull a person's awareness of pain. Ancient Hindu (East Indian) civilizations used henbane (a plant) and wine as well as hemp. In the first century the Greek physician Dioscorides (A.D. 40-90) described the use of wine made from mandragora (a plant known as mandrake) to produce a deep sleep in patients undergoing surgery. Dioscorides used the Greek word "anesthesia" to describe this sleep. And the Greek poet Homer (author of the *Illiad* and the *Odyssey*) referred to the pain-killing effects of the potion nepenthe.

The Greek physician Dioscorides described the use of wine made from mandragora to produce deep sleep in patients undergoing surgery.

Early Anesthetics

Alcoholic beverages such as wine and brandy have long been used to induce numbness. **Opium**, which comes from the poppy plant, also has a long history of use in human cultures. Seeds of the opium poppy have been found in prehistoric Swiss lake dwellings and in Egyptian ruins. Opium was praised by the Persian philosopher and physician Avicenna in the eleventh century as the most powerful of stupor-producing substances. English physician Thomas Sydenham (1624-1689; sometimes referred to as the "English Hippocrates") promoted opium for many medical uses in the 1600s.

Early Arab writings mention anesthesia induced by inhalation. This idea was the basis of the "soporific sponge" ("sleep sponge") introduced by the Salerno (Italy) school of medicine in the late twelfth century and by Ugo Borgognoni (Hugh of Lucca) in Italy in the thirteenth century. The sponge was promoted and described by Hugh's son, surgeon Theodoric Borgognoni (1205-1298). This type of anesthetic involved a sponge soaked in a dissolved solution of opium, mandragora, hemlock juice, and other substances. The sponge was then dried and stored. Just before surgery it would be moistened and held over the patient's nose. The fumes rendered the patient unconscious.

Mechanical methods of inducing anesthetic effects were also explored. Frenchman Guy de Chauliac (1300-1368) employed compression of the nerve trunk in the 1300s, as did another French physician, **Ambroise Paré,** in the 1500s. The ancient Roman practice of bleeding patients into unconsciousness was recommended in 1777 by Alexander Munro II of Edinburgh, Scotland, and put into practice around 1800 by Philip Syng Physick (1768-1837) of Philadelphia, Pennsylvania.

The Modern Era of Anesthesia

The modern era of anesthetics began in the late eighteenth century when chemists began to investigate the use of various gases.

The modern era of anesthesia began in the late eighteenth century when chemists began to investigate the use of various gases. Joseph Priestley (1733-1804) discovered **nitrous oxide** in 1772, and in 1800 **Humphry Davy** (1778-1829) discovered that the gas had anesthetic properties when it was inhaled. In 1818 Davy's student Michael Faraday (1791-1867) determined that inhalation of **ether** had the same effect. Henry Hill Hickman (1800-1830) experimented with both carbon dioxide and nitrous oxide on animals to carry out painless surgery in the early 1820s.

The anesthetic properties of ether and nitrous oxide were quickly adopted by several American dentists and doctors. Georgia physician Crawford Long (1815-1878) performed the first operation under ether anesthesia in 1842. Two years later, a Hartford, Connecticut, dentist named Horace Wells (1815-1848) used inhaled nitrous oxide to **extract a tooth** painlessly. Boston dentist William T. G. Morton (1819-1868) arranged the first public demonstration of ether-anesthetized surgery in 1846. The technique was documented in London, England, just two months after Morton's surgery when Dr. Robert Liston (1794-1847) performed an **amputation** using ether anesthetic. The technique was soon practiced worldwide.

Scottish obstetrician James Young Simpson (1811-1870) experimented with ether, then **chloroform,** to ease the pain of childbirth. Queen Victoria's (1819-1901; ruled England from 1837-1901) use of chloroform for her own deliveries in 1853 and 1857 firmly established the procedure as standard practice. Dr. John Snow (1813-1858), who administered the

A patient in anesthetized before surgery. Today's anesthetist is a highly trained specialist who administers several anesthetics at the same time.

chloroform to the queen, became the foremost authority on anesthesia and is recognized today as the world's first professional anesthetist.

Other Anesthetics

Local anesthesia (deadening only the part of the body being treated) also became important, especially after the invention of the hypodermic **syringe** by Charles Gabriel Pravaz (1791-1853) in 1853. Not long after that, Alexander Wood (1817-1884) of Edinburgh, Scotland, used the syringe to inject pain-relieving **morphine**. Dr. B. W. Richardson (1828-1896) of Glasgow, Scotland, introduced ether spray for freezing tissue in 1866. Carl Koller (1857-1944) demonstrated the use of **cocaine** as a local anesthetic in 1884. Surgeon William Halsted of Baltimore, Maryland, developed the technique of anesthesia conduction by blocking nerve impulses with injections of cocaine. Because of the addictive nature of cocaine, synthetics such as **Novocain** were substituted.

Intratracheal anesthesia, which involves introducing anesthetic through a tube in the trachea (windpipe in the throat), was pioneered by New York City surgeon George Fell (1850-1918) and perfected in 1909 by Samuel Meltzer and John Auer of the Rockefeller Institute. Spinal anesthesia (used to numb the lower half of the body) was experimented with in 1885 by New York City neurologist Leonard Corning (1855-1923), who injected a cocaine solution into his patient's spine. German doctor August Bier (1861-1949) refined the technique in 1898, and Rudolph Matas (1860-1957) of New Orleans, Louisiana, introduced the procedure to the United States in 1899. By the 1920s the use of spinal anesthesia was standard across the United States.

Intravenous Anesthesia

Intravenous anesthesia (the injection of anesthetic directly into a patient's bloodstream) was first attempted by Englishmen Robert Boyle (1627-1691; chemist and physicist) and Sir Christopher Wren (1632-1723; famous architect) around 1659. The duo's injection of a warm solution of opium and sherry stupified their subject, a dog. Johann Major of Germany tried the same technique on a human subject in 1667. The idea was abandoned, however, until about 1874, when Pierre Oré used chloral hydrate intravenously on a dog and, in 1875, a human patient. After **barbiturates** were discovered in the early 1900s—especially after improved substances were developed in the 1920s—the use of intravenous anesthetics was firmly established.

Early in the 1900s American surgeons Harvey Cushing (1869-1939) and George Crile (1864-1943) contributed to the safe use of anesthesia

by monitoring the patient's blood pressure during surgery. Crile and Cushing also combined local (or regional) anesthetics with general anesthetics or with local infiltration anesthesia. Today's anesthetist is a highly trained specialist who administers several anesthetics at the same time and uses sophisticated equipment to monitor a patient's blood pressure, rate of respiration, heartbeat, and blood levels of oxygen, carbon dioxide, and anesthetic vapors.

Angiography, cerebral

Wilhelm Konrad Roentgen's (1845-1923; German physicist and winner of the first Nobel Prize for physics in 1901) discovery of **X-rays** in 1895 revolutionized most fields of science, including medicine. The fact that some parts of the body are more dense than others means that X-rays can be used to diagnose some medical problems. Bone fractures, for example, are easily examined using X-ray photographs.

This generalization is not true, however, for studies of the brain because the brain's density is essentially constant in all its parts. In an attempt to apply X-ray analysis to the brain, Walter E. Dandy (1886-1946) developed a technique for injecting air into brain cavities. The lower density of air made it possible to use X-rays to study normal and abnormal brain structures. The method was not very effective, however, and often involved considerable risk to the patient.

In 1927, Portuguese neurologist Antonio Egas Moniz came up with another solution to this problem. He injected opaque (inpenetrable to the passage of light) liquid solutions into the brain's arteries. Blood vessels in the brain then become clearly visible. The resulting photographs could be compared with photographs of the normal brain to see where tumors may have taken the place of blood vessels. Over the next decade, Moniz and his colleagues published more than 200 papers describing their technique, known as cerebral angiography.

Although several newer brain scanning tools have been developed over the years since Moniz created his technique, including **CAT** (computerized axial tomography), PET (positron emission tomography) and **MRI** (magnetic resonance imaging), angiography still holds its own as a technique for pinpointing injuries and abnormalities of the brain.

Angiography, coronary

Coronary angiography is an **X-ray** of the heart and blood vessels of a living patient. The X-ray is taken with a moving camera, which produces a very detailed and accurate picture of the condition of the coronary arteries. The procedure is considered invasive (involving entry into the living body), because a thin, flexible tube called a catheter is inserted into an artery, usually in the groin. The catheter then must be threaded through the circulatory system to the heart. A dye that will appear on the X-ray film is injected through the catheter while the pictures are taken. The dye may produce a temporary burning sensation, and some patients experience some nausea and possibly an urge to urinate. After the procedure is completed, the patient rests to allow the incision to heal. The patient is also observed to make sure there are no negative reactions to the procedure, such as bleeding, clotting, or sensitivity to the dye.

Researchers had tried since the 1930s to develop a technique for viewing coronary arteries, which is considered necessary for diagnosing and treating coronary artery disease. Early coronary angiography faced two major problems. First, the procedure required that enormous amounts of contrast agent (or dye) be injected, which often caused serious side effects. Secondly, the procedure produced only one radiographic plate. Success became more likely when serial (successive) film changers and image intensifier were introduced in 1949. Film changers allowed for true motion cinematography, or pictures taken with a moving camera.

Until the late 1950s physicians would not allow the dye to enter the heart itself, believing that patients would experience ventricular fibrillation (an irregular contraction of the heart that frequently causes cardiac arrest, or heart attack). In 1958 Mason Sones, a physician at the Cleveland (Ohio) Clinic, was conducting an angiogram on a patient. He intended the dye to go only as far as the aorta (main artery branch that carries blood from the left side of the heart to the arteries of all limbs and organs except the lungs), but the catheter slipped inside the heart. When the patient experienced no ill effects from the dye and the X-ray films were so much better than previous angiography, a new standard was established.

Sones's coronary angiography became widely used. Considered the "gold standard" for diagnosing coronary artery disease, angiography is now done so frequently that it is almost commonplace. But the procedure is very expensive (one 1995 analysis priced angiography at $5,500 per procedure). Doctors have less expensive—and less direct, or non-invasive—ways of assessing the health of the heart, such as an echocardiogram (an ultrasound

of the heart) and exercise tests. A study published in the *Journal of the American Medical Association* (JAMA) in 1992 found that of patients who were told they needed angiography, 80 percent did not actually need it.

Other studies reveal that physicians are not as likely to recommend angiography for their female patients, even when they exhibit the same symptoms as male patients who receive the procedure. More studies need to be conducted to find out whether women are being deprived of the test, or whether they are being handled more appropriately than male patients. In any event, the American College of Cardiology (ACC) and the American Heart Association (AHA) have joined to create specifications on how angiography should be used.

Angioplasty, balloon

If left untreated, atherosclerosis can lead to complications like angina, a condition that causes suffocating heart pain.

Balloon angioplasty is a medical technique used to widen coronary (heart) arteries that have been narrowed by plaque (fatty material) deposits that cling to the inside of the artery walls. In a coronary (heart) disease called atherosclerosis ("hardening of the arteries"), the arteries become so dangerously clogged that surgery is required to clear the blockage. If left untreated, atherosclerosis can lead to complications like angina, a condition that causes suffocating heart pain.

Historical Angioplasty

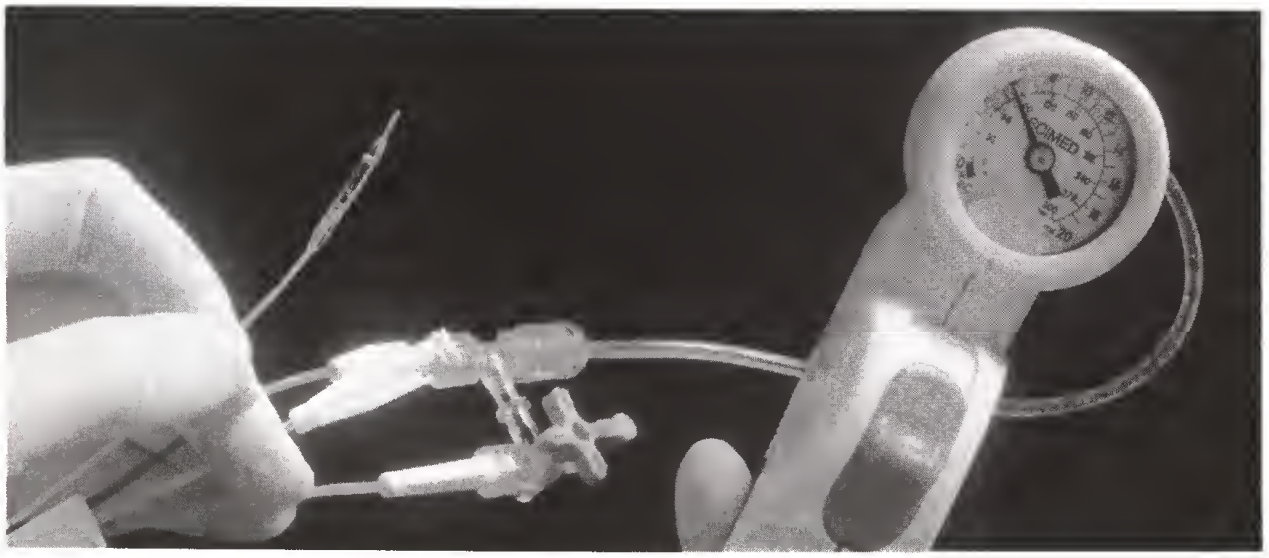
The first step toward relief of atherosclerosis was the invention of cardiac (heart) catheterization (a method for draining harmful fluid build-up). The catheterization procedure was invented by German physician Werner Forssmann (1904-1979) in 1929. Experimenting on himself, Forssmann found a way to thread a catheter (a long, thin, flexible tube) through an arm vein all the way into the heart. In 1958 Mason Sones invented selective coronary arteriography, an **x-ray** procedure in which dye is injected into the arteries. This allows physicians to use X-ray photography to follow the path of the dye through the body. In 1964 Charles T. Dotter and Melvin Judkins of the University of Oregon (Eugene) combined these advances to successfully perform transluminal (along the "lumen," or cavity, of a blood vessel) angioplasty (blood vessel repair). Dotter and Judkins unclogged leg arteries with a fluoroscope (an instrument used for examining the internal structure of an opaque object), which guided a catheter along the artery and dilated (open up) the blocked area.

Swiss Angioplasty Procedure Performed

At the University Hospital in Zurich, Switzerland, Andreas Gruentzig was especially interested in whether the catheterization procedure could be used to clear blockage in the relatively small coronary arteries, the blood vessels that feed the heart. First he added a balloon to the catheter. The balloon-tipped catheter was inserted into the partially blocked portion of an artery. The balloon was then inflated (blown up), which pushed the fatty plaque back against the inner blood vessel walls. Thus the artery was opened, greatly improving blood circulation. Gruentzig then miniaturized the balloon catheter for use in coronary arteries. On September 16, 1977, Gruentzig performed the first coronary balloon angioplasty on a human patient. Gruentzig's surgical team was surprised at the ease of the procedure.

Angioplasty, also known as "Percutaneous Transluminal Coronary Angioplasty" (PTCA), rapidly came into widespread use around the world as a relatively simple, inexpensive, and safe alternative to coronary bypass surgery (a major operation that requires cutting open the patient's chest and usually a leg, from which a vein is harvested, or taken, to be used in the bypass). In contrast, angioplasty presents fewer risks while it saves the arms, legs, and kidneys affected by the impaired circulation.

There has been growing concern, however, about a buildup in the arteries called restenosis that often appears in patients who have undergone balloon angioplasty. A new technique, pioneered by several groups of researchers in the early 1980s, combines **lasers** with the catheter. The laser vaporizes plaque in arteries, then balloon angioplasty finishes the opening of the blood vessel. Laser angioplasty is currently approved for use in leg arteries only. One drawback is that laser angioplasty carries a signifi-



Catheter. Coronary angioplasty rapidly came into widespread use around the world as a relatively simple, inexpensive, and safe alternative to coronary bypass surgery.

cant risk of perforating (puncturing) the blood vessels being treated. Other experimental methods exist for keeping arteries open after balloon angioplasty. They include surgically implanted stents (rods) that physically hold open the vessel, a catheter equipped with a scraper to shave off plaque, and use of sound waves to remove plaque.

[*See also* **Angiography, Coronary; Laser surgery**]

Antabuse

Antabuse, also known by its scientific name disulfiram, medication was approved by the U.S. Food and Drug Administration (USDA) in 1951 for the treatment of alcoholism. Antabuse discourages a drinker's desire for alcohol by causing extremely unpleasant symptoms when a drink is taken.

Disulfiram was discovered by accident in 1947 at the Royal Danish School of Pharmacy in Copenhagen, Denmark, by Danish researchers Eric Jacobsen (1903-) and Jens Hald. The duo was studying compounds for possible use in treating parasitic stomach infections. One of the compounds was disulfiram. As was common among researchers at the time, both men took a small dose of disulfiram to check for possible side effects. At a cocktail party several days later, Jacobsen and Hald became very ill after having a drink. Because each man experienced the same symptoms at the same time, the researchers concluded that the disulfiram, triggered by the alcohol, was responsible for the illness. They quickly conducted a study to confirm their findings, publishing it the same year.

Antabuse disrupts the body's processing of alcohol in the liver. Normally, certain enzymes (proteins produced by living organisms) break down alcohol into acetaldehyde, while other enzymes break acetaldehyde down into acetate (a salt of of clear, colorless organic liquid). Disulfiram blocks the breakdown of acetaldehyde, resulting in a rapid rise of this chemical in the blood. A patient experiencing an disulfiram-ethanol reaction can develop a severe headache, difficulty in breathing, chest pains, vomiting, and a drop in blood pressure. Very rarely, the reaction can result in death. The severity of symptoms depends in large part on the amount of alcohol taken.

Ruth Fox, a New York City psychoanalyst, was the first American to use antabuse for the treatment of alcoholism. She began treating 50 patients with the drug in 1949, but had to reduce the dosage after her

patients reported serious side effects. Fox cut the dosage and counseled patients on the severe reactions that could result from drinking. She found that antabuse was effective in deterring drinking among alcoholics and went on to treat about 2,500 patients with it. Today, approximately 200,000 people take antabuse daily in the United States. A 1980 study reported, however, that alcoholics taking antabuse could get a euphoric reaction if they consumed small amounts of alcohol, thereby conditioning them to continue their addictive behavior. More recent research has indicated that the drug is most effective for older patients who tend to relapse more frequently, and that the patient's motivation to take antabuse is very important to its effectiveness.

Antibiotics

Antibiotics are medications taken to fight infections caused by bacteria. When they first became available during World War II (1939-1945), antibiotics were called "wonder drugs" because of their stunning record for safety and effectiveness. Well-known antibiotics include **penicillin, streptomycin,** and erythromycin. Antibiotics are usually taken orally (by mouth) or given as **inoculations.**

When they were first discovered during World War II, antibiotics were called "wonder drugs" because of their stunning record for safety and effectiveness.

How Bacteria Make Us Ill

Bacteria are single-celled organisms that exist everywhere in nature and can have beneficial purposes. Most bacteria are harmless to humans. Disease may result, however, when an infectious type of bacteria enters the human body, by way of the nose or mouth or through a wound. Many types of bacteria reproduce by cell division (the one-celled organism divides into two identical organisms), a very rapid process that sometimes takes as little as 20 minutes. The chemicals bacteria release may be toxic (poisonous) to human cells or may interfere with cell function. Bacteria are responsible for such debilitating and even fatal human diseases as pneumonia, typhoid fever, Rocky Mountain Spotted Fever, and tuberculosis.

Antibiotic drugs are prepared from natural compounds that are antagonistic (harmful) to bacteria. Some fungi and benign (harmless) bacteria can defend themselves against harmful bacteria by producing chemicals that destroy bacterial cells. Scientists and researchers have created many effective drugs for human use out of such bacteria as mold in the Penicillium family or *Streptomyces griseus*. These anti (against) biotic (life) com-

pounds usually work by either damaging the harmful bacteria's cell membrane (the thin layer of animal or plant tissue that covers an organ or bodyily fluid) or preventing its growth.

Fleming Discovers Penicillin

Scientists of the early 1800s first classified bacteria. In 1829 they established the name *Bacterium* as their genus (a grouping of species with common origins). Bacteriology was an experimental science that emerged slowly until a major breakthrough occurred in 1928 that led to the development of **penicillin.** Scottish doctor **Sir Alexander Fleming** (1881-1955; winner of the 1945 Nobel Prize in medicine with **Howard Walter Florey** and **Ernst Boris Chain**) was growing colorful patches of bacteria in covered dishes in his crowded St. Mary's Hospital Medical School laboratory. He noticed that a green mold had gotten into one of the dishes. Fleming knew that mold spores traveled through the air and could easily land and grow in any dish left uncovered. In this particular dish the bacteria closest to the green mold seemed to have disappeared or dissolved. Fleming examined the mold carefully and photographed it. An associate identified the growth as *Penicillium notatum.*

Curious about how the bacteria in this dish were killed, Fleming took the greenish "fluff" in the dish and made a mixture that his laboratory workers called "mold juice." Fleming named the juice "penicillin" and gave it to some laboratory mice. He found that the penicillin killed only the harmful bacteria and not the healthy cells in the mice. This made Fleming's "mold juice" safer than any other known bacteria-killing substances. It was an incredible discovery. If this mold mixture could be made into a drug, then someone with an infection could be cured of disease without being harmed by the cure.Unfortunately, Fleming ran into difficulties turning penicillin into a drug because he was unable to purify and concentrate the substance.

Further Breakthroughs

The next breakthrough came in 1939 from scientists studying microorganisms in soil and how these organisms helped to keep soil healthy. In 1939 American soil microbiologist Selman Abraham Waksman (1888-1973; winner of the 1952 Nobel Prize for medicine) was analyzing the antibacterial properties of soil organisms. Working on streptomycetes fungi at Rutgers University laboratory in Newark, New Jersey, Waksman invented the term "antibiotic" to describe a compound that would harm bacteria without being toxic to human cells. He isolated (separated)

antibacterial agents from the streptomycetes, but he found them all to be toxic to human cells.

In 1940 Florey (1898-1968; professor of pathology originally from Australia) and Chain (1906-1979; German biochemist who had fled Hitler's Germany) began to experiment with penicillin at Oxford University in England. After many experiments, the duo succeeded in purifying penicillin and began testing it on mice. When penicillin caused few side effects in the mice, Florey and Chain began testing it on humans. With the outbreak of World War II (1939-1945), wounded were crowding into hospitals. Florey and Chain's team of workers rushed to develop penicillin in large quantities to fight bacterial infections.

By 1942 penicillin was being mass produced by British pharmaceutical companies. Through the distribution of penicillin, many soldiers were saved from the infections that developed after they were wounded in battle. Penicillin also reduced the rate at which people died from bacterial pneumonia. Where once pneumonia killed 60 to 80 percent of the people who came down with the lung infection, penicillin lowered the rate to 1 to 5 percent.

Through the distribution of penicillin, many soldiers were saved from the infections that developed after they were wounded in battle.

Other Developments

Despite its effectiveness, penicillin did not cure every bacterial infection. Eventually scientists understood that the drug worked only against *Gram-positive* bacteria (a range of bacteria that reveal a blue stain in certain laboratory tests). During the early 1940s Waksman focused on *Gram-negative* bacteria (a range of bacteria that loses the blue stain). He eventually found a nontoxic compound derived from *Streptomycetes griseus* mold which he named "streptomycin." In January of 1944, he announced that this antibiotic could work against both Gram-positive and Gram-negative bacteria and was particularly effective against tuberculosis.

Initially made only from natural substances, antibiotics were soon formulated from synthetic (non-living) or partly synthetic materials. In 1945 Benjamin Dugger, Y. Subbarow, and A. Dornbush discovered **aureomycin,** the first of the class of antibiotics known as tetracyclines. John Ehrlich and Quentin Bartz isolated another soil microbe in 1947 that chemists at Parke Davis & Company found could be synthesized (made) into an antibiotic. The new drug, chloramphenicol (an antibiotic that is antagonistic, or harmful, to a wide spectrum of bacteria), became one of the first bestselling synthetic drugs. Other synthetic antibiotics include terramycin, erythromycin, and bacitracin.

Penicillin is packaged in a sterile atmosphere maintained by ultraviolet light. Operators must wear protective clothing that includes goggles and head coverings.

Taking Antibiotics

Antibiotics may be injected with a needle and syringe or taken by mouth in pill or liquid form. They prevent bacterial cells from growing or dividing normally. For example, penicillin prevents bacteria from forming their cell walls. The compound in the antibiotic mimics (acts like) similar compounds in the bacterial cell wall. But when the antibiotic becomes part of the bacterial cell wall, it leaves a gap. The bacterium's cell contents are no longer properly encased and protected, so the contents spill out and the cell dies.

For centuries, medical practitioners used leeches to suck blood from patients.

Resistant Bacteria

An antibiotic may be very effective in halting the reproduction of bacteria at first. There are always some bacteria, however, that are naturally resistant to the drug. Soon the resistant strain is able to catch up and reproduce in strong numbers. Antibiotic resistance was noticed as early as the 1940s. Some authorities believe that overuse of antibiotics causes bacteria to become resistant. One example of overuse is in factory farming of poultry and livestock, in which antibiotics are routinely administered to animals as a preventive medicine to keep them from getting sick. Eventually, the antibiotics may fail to work because the infection is caused by resistant bacteria.

The same phenomenon can be observed in humans. The U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, reported in January of 1996 that deaths from infectious diseases are on the upswing. According to the report, death from infectious diseases rose 58 percent between 1980 and 1992. (In 1980 infectious diseases caused 41 out of every 100,000 deaths. In 1992 infection was responsible for 65 out of every 100,000 deaths.) The CDC claims that antibiotics have been overprescribed and improperly prescribed, which results in resistant bacteria (bacteria exposed to, but not killed by, antibiotics can mutate to make themselves immune to antibiotics). The resistant bacteria can then pass their resistance to other bacteria. When the resistant microbes produce illness in humans, antibiotics that have traditionally cured that disease no longer work.

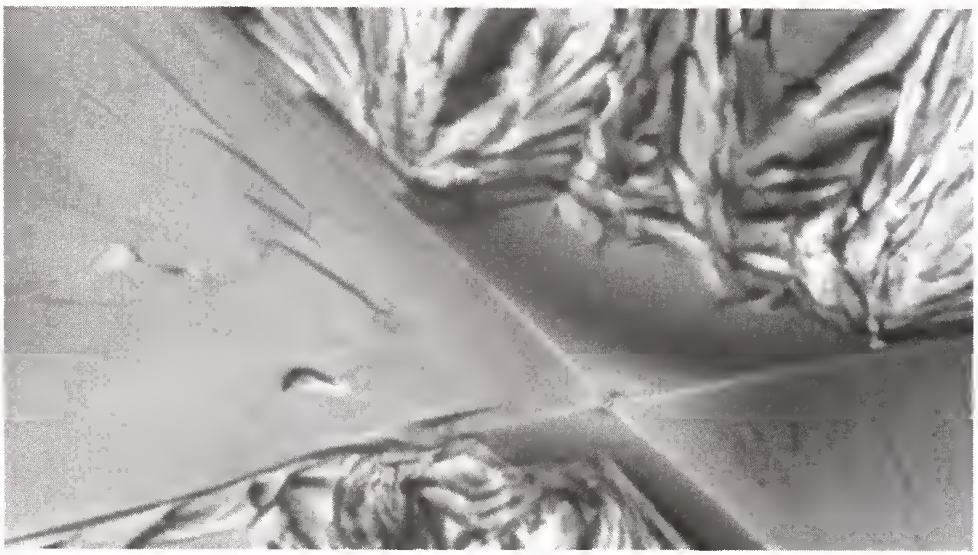
The CDC predicts the possibility of a post-antibiotic era—a time when antibiotics no longer work—and advises that antibiotics be used very carefully and only according to directions. Furthermore, before prescribing antibiotics, health care providers should first take a sample of the bacteria (which is then grown in a culture). This allows the bacteria to be clearly identified and indicates exactly which antibiotic should be prescribed.

Anticoagulant

Anticoagulants are substances that inhibit coagulation (clotting) of the blood. They are used to keep stored blood for **transfusions** from clotting, to treat conditions involving dangerous blood clotting (includings strokes and heart disease), and in situations where there is a serious risk of dangerous clotting, such as during certain surgical procedures.

For centuries, medical practitioners had used leeches to suck blood from patients. In 1884 J. B. Haycraft showed that blood flowed freely during this procedure because the leeches secreted an anticoagulant (anti-clotting) factor. A dry, powdered extract of leeches' heads called *hirudin* was introduced around 1900 and used in physiological experiments (tests relating to the functioning of the human body), although it was not used in clinical practice. New research on hirudin in the 1990s has led to an experimental drug shown to be safe and effective. Although production of this substance is currently expensive, it may eventually provide another anticoagulant option.

Prior to the discovery of hirudin, donated blood tended to clot before it was absorbed into the recipient's blood system; as a result, transfusions were not always effective. In 1869, sodium phosphate was introduced as an anticoagulant to overcome this problem. In 1914 sodium citrate was also shown to be an effective anticoagulant for donated blood. Sodium citrate's use was of great value during World War I (1914-1918) and became the standard by 1917.



The anticoagulant sodium ciltrate. Today, the most commonly used anticoagulants are heparin and coumarin.

Heparin

The main anticoagulants used today, are heparin, which is injected, and *coumarin*, which is taken orally (by mouth). Heparin was discovered in 1916 by Jay McLean (1890-1957), a medical student. McLean was studying at Johns Hopkins University under William Howell (1860-1945), who had been investigating blood coagulation for years. McLean took on the project of preparing pure samples of cephalin, a clotting substance obtained from brain tissue. While extracting compounds similar to cephalin from heart and liver tissue, McLean discovered that the liver extract did not cause blood to clot. McLean called the extract *heparphosphatid*.

After McLean left Johns Hopkins, Howell continued working on the liver extract, aided by Emmett Holt (1855-1924). The researchers developed ways to extract an improved water-soluble anticoagulant from liver, which they named heparin in 1918. Howell continued his work on heparin during the 1920s, while Charles Best (1899-1978), David Scott, and Arthur Charles of the University of Toronto worked with heparin extracted from beef liver. They eventually developed practical methods for purifying and standardizing the drug. Clinical trials followed. The success of the **artificial kidney** in 1944 and the later development of heart-lung bypass procedures depended on the use of heparin to prevent fatal blood clotting. Heparin then came into standard use, although it does carry a possible risk of excessive bleeding.

Coumarin and Warfarin

Oral anticoagulants have their origins in an odd bleeding disorder in cattle that broke out in North Dakota and Canada in the 1920s. Cattle in these areas that ate hay made from spoiled sweet clover had a tendency to bleed to death. F. W. Schofield, a Canadian veterinarian, traced the deaths to clover in 1922. In 1931 a North Dakota veterinarian, L. M. Roderick, found that the hemorrhaging was caused by the reduced activity of *prothrombin*, a clotting factor in blood. Isolating prothrombin proved to be very difficult, but it was finally accomplished in 1939 by Karl Link and H. A. Campbell of the University of Wisconsin agricultural college. The clotting factor in prothrombin turned out to be *dicumarol*, a coumarin (a fragrant organic substance often extracted from tonka beans) compound that had originally been synthesized in an impure form in 1903.

A potent synthetic form of dicumarol was originally introduced as an extremely effective rodent poison.

In 1948 a potent synthetic form of dicumarol was originally introduced as an extremely effective rodent (small mammals of the order *Rodentia*, which includes rats, squirrels, and beavers) poison called *warfarin* (named for the patent holder, Wisconsin Alumni Research Foundation). Although warfarin rapidly became very popular worldwide as a rat

poison, medical practitioners hesitated to use it on patients because it seemed so toxic (poisonous). This viewpoint changed after a United States army recruit unsuccessfully attempted suicide in 1951 by taking massive doses of warfarin-based rat poison. Warfarin is now the most widely prescribed oral anticoagulant.

Recent Developments

Research from the 1970s to 1990s has shown that the common painkiller **aspirin** has anticoagulant properties. In fact, doctors have recommended it for preventing blood clots near the heart. Apirin's fairly narrow in its effectiveness, however, and does not work as well to prevent strokes, blood clots in the legs, or clotting during surgery. Unfortunately, in order to do their job, anticoagulants suppress the human body's natural clotting process, which is used to heal wounds. Those patients on anticoagulants must always beware of excessive bleeding while taking the medication.

[*See also* **Artificial kidney**]

Antihistamine

Antihistamines are drugs used to relieve the symptoms of allergies caused by histamine, an organic (natural, basic) compound made from the amino acid histidine. Histamine is released from certain cells when the body is irritated by outside substances, such as pollen, or if the body thinks that a certain food is an enemy rather than a friend. The body then tries to expel the perceived invader by swelling tissues and creating the typical symptoms of an allergic reaction, such as sneezing, hives (skin rashes), or in the case of food allergies, stomach upset and diarrhea as well. Histamine was first recognized and suggested as the cause of allergic reactions by Henry Dale (1875-1968) and Patrick Playfair Laidlaw (1881-1940) in 1910. By 1932 histamines were confirmed as causative agents in allergic response.

Bovet's Research

Researchers then sought to find substances that could counteract the effects of histamines. Swiss-born Italian pharmacologist Daniel Bovet (1907-; winner of the 1957 Nobel Prize for medicine) of the Pasteur Institute in Paris, France, focused on this problem in 1936. Since histamine is extremely toxic except when introduced to the body by absorption through the intestine, Bovet reasoned that histamine must normally exist in the

body in combination with a neutralizing agent (a substance that renders other matierial inactive or ineffective). Only "free" histamine would produce allergic symptoms, so an antagonist (opposite) to this free histamine had to be found. Bovet could not discover a natural antagonist to histamine, so he looked for substances that were similar in chemical structure to it, to see if they had antagonists that might be modified to work against histamine. Because the two hormones adrenaline and acetylcholine are structurally similar to histamine, Bovet investigated two groups of substances called sympatholitics and parasympatholitics, which block the effects of adrenaline and acetylcholine. This approach proved fruitful, and in 1937 Bovet and his research student Anne-Marie Staub succeeded in synthesizing the first antihistamine. This first attempt was too toxic to use in humans, however, so from 1937 to 1941 Bovet conducted thousands of experiments to produce a usable antihistamine. He succeeded with pyrilamine, which was introduced to the public in 1944.

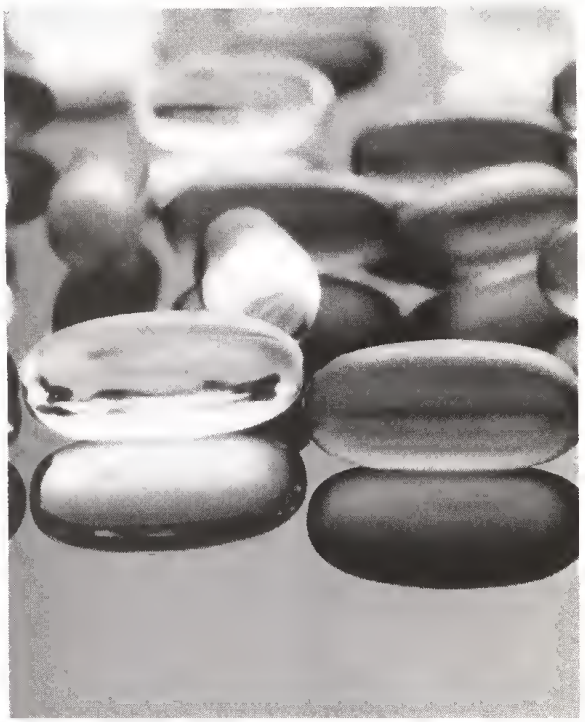
The nature and use of antiseptics was not fully understood until the discovery of bacteria.

Bovet's work laid the foundation for the safe, effective synthesis of antihistamines. In further developments, Bernard N. Halpern, a French research biologist and physician, described the use of phenbenzamine in 1942. And in 1943 a young lecturer at the University of Cincinnati named George Rieveschl developed diphenhydramine, better known as Benadryl.

Beyond Allergy Relief

Once developed, antihistamines became wildly popular. They were promoted by rival drug companies for relief of symptoms of the common cold as well as allergies. Debate still continues in the scientific community on the actual effectiveness of antihistamines against cold virus symptoms. They seem to provide only minor relief on their own, except for clemastine (in found in Tavist-1 and Tavist-D), which may provide modest relief of cold symptoms. Another function for antihistamines was discovered by accident in 1947 when an allergy patient took an antihistamine called Dramamine and unexpectedly found that for the first time in years, she did not suffer from motion sickness when she rode a streetcar.

[*See also* **Adrenaline; Hormone**]



Antihistamine gel capsules. Antihistamines have been promoted for both the relief of allergies and cold virus symptoms.

Antisepsis

Antisepsis is the destruction or inhibition of (slowing the growth of) microorganisms (very small living substances invisible without a **microscope**) that exist on living tissue. Antiseptics are the substances that kill or prevent the growth of the microorganisms. The name comes from the Greek words anti (against) and sepsis (decay). Antiseptics prevent infection and other changes in living tissue by destroying or slowing the growth of germs (microorganisms that cause disease). The nature and use of antiseptics was not fully understood until the discovery of bacteria.

When the skin is broken by a scratch or burn, microorganisms often begin to grow in the wound. Bacteria, viruses, and fungi that may be present on healthy skin can multiply rapidly where the skin is broken. Unless this growth is prevented or stopped, serious infection can take place. Organisms may also enter the body at the site of an injury and cause illness. To prevent this, antiseptics are applied to control the infective growth until the injury heals.

Antiseptic History

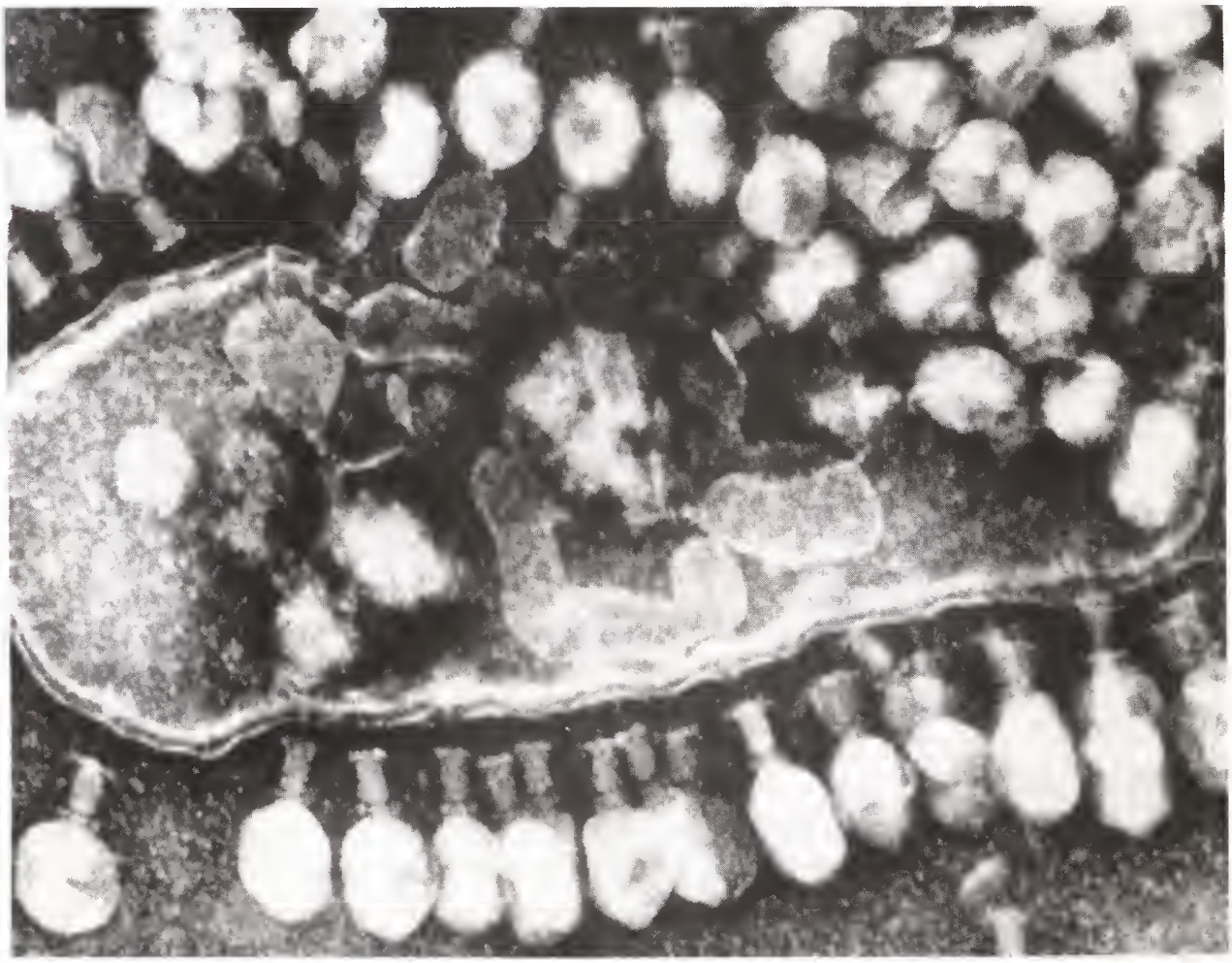
Since ancient times, physicians and healers have been aware of the anti-infective and anti-spoilage properties of certain substances. Egyptian embalmers (people who preserved and prepared bodies for burial) used resins (an organic substance taken from plants and trees), naphtha (a liquid hydrocarbon often used as a solvent or diluting agent), and liquid pitch, along with vegetable oils and spices. The effectiveness of this mixture is shown in the fine state of preservation of Egyptian mummies. Persian laws instructed people to store drinking water in bright copper vessels. The ancient Greeks and Romans recognized the antiseptic properties of wine, oil, and vinegar. The use of wine and vinegar in the dressing of wounds dates back to the Greek physician **Hippocrates** (460-377 B.C.). Balsam, an antiseptic of both southeast Asia and Peru, was introduced to Europe in medieval times and remained in use through the 1800s.

A thirteenth-century surgeon, Theodoric of Bologna, recommended dressings dipped in wine to ward off the development of pus in wounds. English physician Sir John Pringle (1707-1782) published a series of papers entitled *Experiments Upon Septic and Antiseptic Substances* that contain one of the first uses of the word antiseptic. Genevieve Charlotte d'Arconville introduced the use of chloride of mercury as an antiseptic in 1766. After Bernard Courtois (1777-1838) discovered **iodine** in 1811, it became a popular antiseptic treatment for wounds.

None of these antiseptics, however, was sufficient to prevent the almost certain infection of wounds, particularly following surgery. **Amputations**, for example, were common in the 1800s, especially in the case of compound fracture (bone breaks that injure surrounding soft tissue). Amputations had a 40 to 45 percent mortality rate. The introduction of **anesthesia** in 1846 made the problem worse. It permitted more complicated and lengthy surgical operations, greatly increasing the likelihood of infection.

Puerperal Fever

Another deadly form of infection was puerperal (occurring at the time of childbirth) fever, a streptococcus infection of the uterus that struck women who had just given birth. As more women gave birth at hospitals, epidemics of puerperal fever raced through maternity wards, sharply increasing maternal death rates. Most obstetricians (doctors who treat pregnant women) were baffled by the causes and possible prevention of this



A bacteria sample. Until the relationship between bacteria and disease was discovered, doctors paid little attention to surgical cleanliness.

fever. The reason for this epidemic of lay in a lack of knowledge about the existence of bacteria until **Louis Pasteur**'s (1822-1895; discovered the connection between bacteria and disease) work. Physicians—surgeons in particular—had no concern for cleanliness. They wore unwashed street clothes or filthy operating gowns, used unclean instruments, and did not wash their hands before examining or operating on patients, even after examining an infected corpse. Many doctors took pride in the accumulation of blood and pus on their medical garments.

Attempts to understand and stop puerperal fever brought about some of the early advances in antisepsis. In 1773 Dr. Charles White (1728-1813) of England recommended antiseptic injection in some cases of childbirth. Scottish physician Alexander Gordon (1752-1799) stated that obstetricians should wash their hands and clothes before treating patients. American physician and author Oliver Wendell Holmes (1809-1894) presented his conclusions about the spread of puerperal fever by unwashed doctors in 1843, while Hungarian doctor Ignaz Semmelweiss made the same discovery in 1847. When Semmelweiss required his students to wash their hands in an antiseptic chloride solution before examining patients, maternal death rates plunged from a high of 18 percent to a low of nearly 1 percent. Semmelweiss was correct about the transmission of infectious materials, but he could not explain what those substances were. Pasteur had part of the answer. In his studies of fermentation (organic transformation), Pasteur proved the existence of airborne microorganisms.

Lister's Work

English surgeon **Joseph Lister** (1827-1912; professor at London's King's College Hospital) applied this new knowledge of bacteria to develop a successful system of antiseptic surgery. Concerned about the high rate of infection after surgery, Lister studied wound healing with the use of a microscope. After reading Pasteur's work, Lister concluded that microorganisms in the air caused the infection of wounds. Drawing on a report of the effects of carbolic acid on sewage bacteria, Lister developed an antiseptic system using the acid. He sprayed a wound and surrounding areas to destroy infectious organisms and also protected the area from new invasion by bacteria by using multiple-layer dressings. Lister first used the method successfully in an operation on a compound fracture of the leg in 1865.

The Apgar Score is a rating system used to evaluate the health of newborn infants in five categories.

Lister's antiseptic method was not simple, but it was effective. A published account of his successful application of the technique appeared in *The Lancet* in 1867 and ignited controversy (especially since Pasteur's germ theory of disease was still in dispute). Nevertheless, Listerian antiseptic surgery gained supporters worldwide, especially in Germany, where

the technique was applied somewhat successfully in treating soldiers during the Franco-Prussian War (1870-1871). Doctors in the United States were especially resistant to the practice of antisepsis. Widespread acceptance came in the 1890s after German bacteriologist Heinrich Koch (1843-1910) effectively proved that germs cause disease.

Modern Antisepsis

A final obstacle to surgical antisepsis was the human hands. Although surgical instruments and dressings can be sterilized, surgeons' and nurses' hands can only be washed with antiseptics. An American doctor, William Halsted, solved this problem in 1890. Halsted received his medical degree from Columbia University in 1877. He returned to the United States from two years of study in Europe as a convert to the Listerian method of antisepsis. After breaking an addiction caused by his experiments with **cocaine** as an anesthetic, Halsted became chief of surgery at Johns Hopkins Medical School. There, he pioneered the use of rubber gloves in surgery to protect his head nurse, Caroline Hampton, from the antiseptic that was irritating her hands. Today sterile gloves are required during all surgical procedures.

Modern methods of preventing infection are very different from the techniques used by Lister and others. **Antibiotics, penicillin,** and sulfa drugs fight infection internally, and aseptic methods such as sterilization prevent bacteria from existing in a given area. Nevertheless, antiseptics continue to be important and are a lasting monument to Lister's vision. Among the most important used today are iodine, boric acid, and alcohol.

[*See also* **Adhesives and adhesive tape; Surgical instruments**]

Apgar score

The Apgar Score is a rating system used to evaluate the health of newborn infants. The test is administered one minute after birth and again five minutes after birth. A rating of zero, one, or two is given in each of these five categories: color, breathing, heart rate (pulse), muscle tone, and response to stimulation. A total score of three or lower is a signal that the baby's condition is critical and requires immediate attention. A score of seven or higher means that the baby's initial vital statistics are good. Studies of the extended Apgar Score (the five-minute recheck) have shown the test to be a fairly reliable indicator that the subject infant has a good chance for survival.

Because the Apgar Score does not check for all possible complications (such as chromosonal damage), however, a high number does not guarantee that a child's long-term outlook is completely positive.

Apgar Develops System

Until the early 1950s, physicians had no reliable way to assess the health of newborns in the critical first minutes of life. Because of delays in diagnosis, conditions that might have been corrected sometimes proved fatal. In 1952 Virginia Apgar (1909-1974), a physician at the Columbia-Presbyterian Medical Center in New York City, developed a scoring system that became the standard tool for evaluation of newborns. Apgar was one of the first female graduates of Columbia University's College of Physicians and Surgeons; she was also the first woman ever to hold a full professorship at the college. She invented her scoring system after years of studying the effects of **anesthesia** in childbirth.

Apgar Scoring

The Apgar Score has five important components, each with its own set of acceptable standards. The individual categories and their ranges are listed below:

- *Color*: A baby who possesses a healthy pink skin tone receives two points, while a pale or bluish infant receives zero points. Most newborns have pink bodies and lips but bluish hands and feet. This coloring receives one point. An all-over bluish color can mean the baby has problems with his heart or lungs, has something blocking his airway, or has inhaled amniotic fluid.
- *Breathing*: A newborn should gasp and begin to breathe at birth. Regular breathing gets a score of two, while irregular breathing gets a score of one. A score of zero is given to a newborn who makes no effort to breathe. Irregular breathing can mean the infant lacks oxygen in his body, has an infection, has central nervous system damage, or has a depressed respiratory drive because of anesthesia given the mother during birth.
- *Pulse*: The normal heart rate at birth is between 120 and 160 beats per minute. A newborn with no detectable heartbeat is scored at zero; a heart rate of less than 100 beats per minute is scored one, and a two is given for a heart rate of 100 beats per minute or more.
- *Muscle tone*: An infant should move his arms and legs at birth. Limpness or poor muscle tone are usually caused by lack of oxygen, central nervous system trauma, or drugs given the mother during birth. A limp

newborn is scored at zero. Some movement gets a score of one, and active movement gets a score of two.

- *Response to stimulation*: A newborn is stimulated at birth by inserting a tube through a nostril into the throat. This should cause the infant to grimace, cough, or sneeze. If he does not respond he is scored at zero; a grimace alone gets a one, and a grimace with a cough or sneeze is scored at two.

The highest possible total Apgar Score is ten. It is not unusual for infants to score a seven at one minute of age and nine or ten at five minutes of age. By this later time, babies generally have a healthier skin tone and are breathing better. With information provided by the Apgar Score, medical personnel can take immediate measures if needed to assure a newborn's survival.

Arc lamp

Long before the incandescent (very bright) electric light bulb was invented, arc lamps gave birth to the science of electric lighting. When the first large batteries were being built in the early 1800s, researchers noticed that electric current would leap across a gap in a circuit, from one electrode (a terminal that conducts current, such as an anode or cathode in a battery) to the other. The result was a brilliant light.

Collier and Baker patented this electric arc lamp design in 1858.

English chemist **Sir Humphry Davy** (1778-1829; inventor of the miner's safety lamp, also called the "Davy Lamp"; elected president of the prestigious Royal Society in 1820) is credited with discovering this electric arc and inventing the first arc lamp, which used carbon (a nonmetallic chemical element found in many inorganic and organic, or living, things) electrodes. Until the development of the dynamo electric (having to do with the production of electrical energy from mechanical energy and vice versa) generator, the arc lamp was merely a curiosity. It required expensive batteries or generators to operate, and was difficult to control because the light fluctuated too much. In the latter part of the

nineteenth century, improvements were made to the controls and electric current for the arc lamp, but newer inventions—including the incandescent light bulb and discharge lights (such as mercury vapor light and fluorescent lights)—were able to provide consistent light without the excess heat of arc lamps.

The Arc Lamp Today

The arc lamp has found a home for the future, however, in support of certain medical procedures. Lasers and arc lamps often work together to help stop chronic (recurring or happening for a long time) nosebleeds and other non-healing wounds. In addition, arc lamps are used in **laparoscopic surgery** (where small incisions are used and a small video camera guides the surgeon) to provide light for the procedure.

Arteriography, coronary

Coronary heart disease occurs when the arteries near the heart start to narrow due to the build up of a substance called plaque.

Coronary arteriography, the **X-ray** photography of coronary arteries in a living patient, is a technique researchers have tried to develop since the 1930s. The ability to view coronary arteries (the two artery "branches" from the aorta that supply blood to the heart muscle) is considered fundamental to the development of effective diagnosis and treatment of coronary artery disease (also known as arteriosclerosis, or "clogged arteries").

Coronary artery disease occurs when the arteries near the heart start to narrow due to a buildup of a substance called plaque. The heart has to

Arteriography allows doctors to view the coronary arteries of living patients. This procedure can aid in heart disease diagnosis and treatment.

Arteriosclerosis

Arteriosclerosis is a very old disease. It occures when abnormally high levels of cholesterol (a fatty alcohol) and other lipids in the blood leave deposits on arterial walls. The disease is especially common in industrialized nations, where treatment procedures have been slow to develop. Lifestyle change is the most widely recommended remedy. These changes may include a low-cholesterol diet, no smoking, weight loss, and a physician-supervised exercise program.

work harder to pump blood through the clogged opening. An artery can eventually become totally blocked, stopping blood flow to and from the heart, causing cardiac arrest (the most severe form of heart attack). In order to treat the disease before a heart attack occurrs, physicians needed to see how clogged the arteries actually are.

Early attempts at coronary arteriography were hindered by two major problems. First, massive amounts of contrast agent, or dye, had to be injected into patients. This often caused serious side effects. Secondly, only a single radiographic plate was obtained for each injection. Improvements to the process came with the introduction of serial film changers in 1949 and the image intensifier in 1949, which allowed true motion cinematography. The technique remained less than ideal, however, until 1958, when an accident led Mason Sones to the development of selective coronary arteriography.

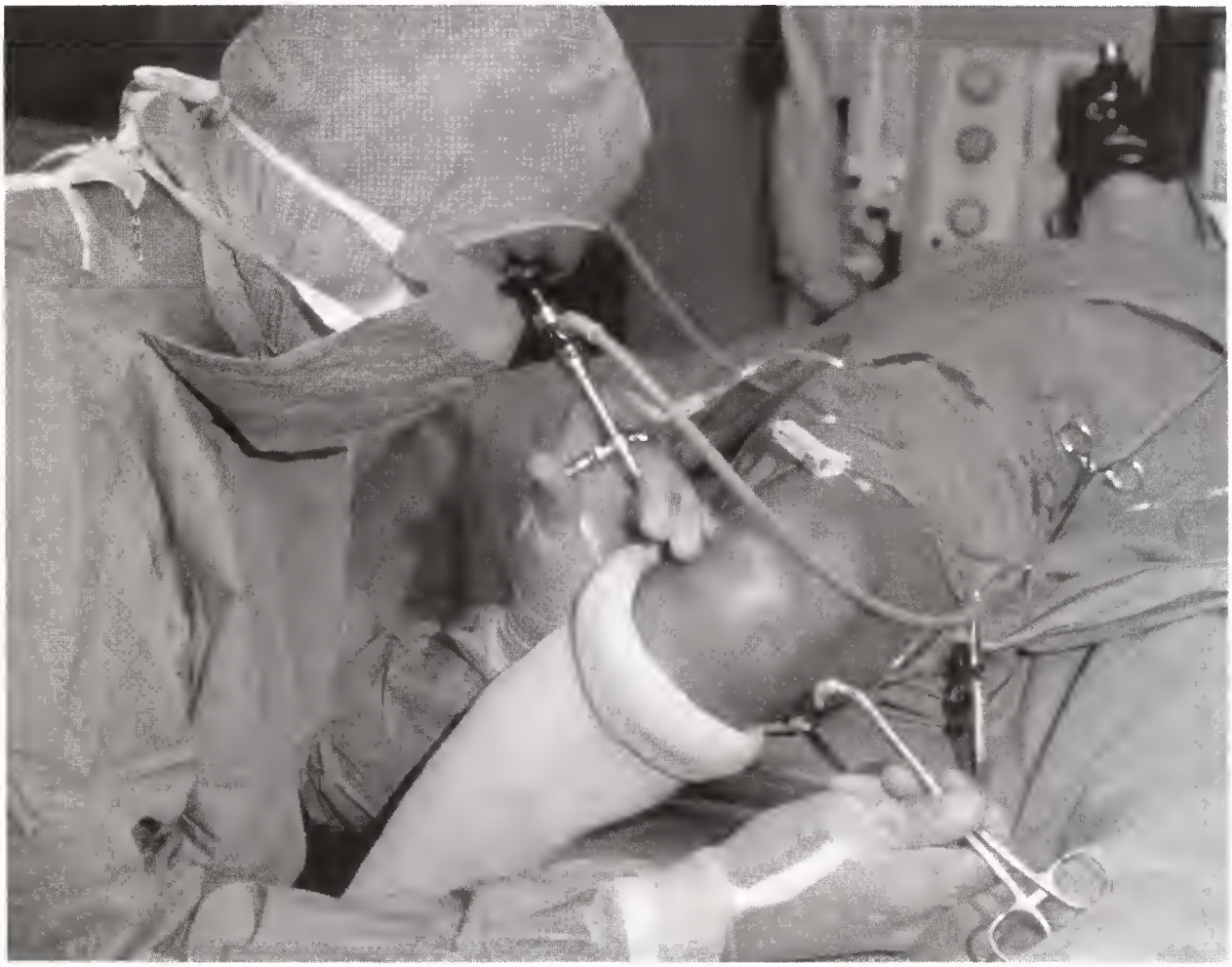
Sones Makes a Discovery

Sones was working in his laboratory at the Cleveland Clinic with a huge, heavy image amplifier that required the physician to stand in a pit beneath the patient's table while an assistant on the platform above injected the contrast agent via a catheter (a slender tube inserted into the body for the passage of fluids). The injection was supposed to be made into the aorta, a major blood vessel, rather than the heart itself. This was because the direct-heart injection could cause the heart to go into ventricular fibrillation (an irregular contraction that frequently causes cardiac arrest). The catheter slipped, and Sones was horrified to see the injection travel into the coronary artery itself. Fully expecting the patient to go into fibrillation, Sones was very surprised when the patient did not. The physician concluded that selective doses of smaller, more diluted amounts of contrast agent—introduced directly into individual coronary arteries—would finally make consistently clear arteriography of selected coronary arteries possible.

After other researchers improved the technique and catheter design, Sones's coronary arteriography became widely used. It helped thousands of patients to receive effective treatment of accurately diagnosed coronary artery disease.

Arthroscope

The arthroscope is an optical (pertaining to the eye) instrument that allows doctors to view the inner workings of a moveable joint without having to perform surgery. The instrument is a flexible narrow tube containing several bundles of hair-thin glass fibers that are covered with a reflective coating. A highly intense light source, usually a halogen lamp, is used to transmit light along one bundle of fibers toward the target area inside the joint (a place where two bones are joined, usually so that they can move).



Doctors perform arthroscopic knee surgery on a patient. Because there is less damage to the surrounding tissue, arthroscopic procedures usually allow patients to heal faster.

Another bundle of fibers carries an image of the target area back up the tube where it is viewed through an eyepiece.

Crude versions of the arthroscope were used as early as the nineteenth century and included long, rigid tubes illuminated by candles. The first efforts to develop the kind of glass fibers that would eventually be used in arthroscopes were made by the Atomic Energy Authority and the Rank Organization in England. By 1965, a 25-micron (a micron is one-thousandth of a millimeter) fiber had been produced which was quickly followed by the development of a 15-micron (a much finer) fiber. When the American Cytoscopic Company succeeded in sterilizing glass fibers, the possibilities for medical uses of the arthroscope increased greatly.

The modern arthroscope contains additional features in the form of air and water channels for flushing water through or inflating targeted areas. Miniature instruments can be placed at the tip of the arthroscope to perform simple operations. Used with a **laser** beam, the instrument can control localized bleeding. Because the size of the incision (cut) needed to insert the arthroscope is small, surgery within a joint is less traumatic for patients. With less damage to the surrounding tissue, patients heal faster and regain use of their joints with less pain and in less time.

[*See also* **Endoscope**]

Artificial blood

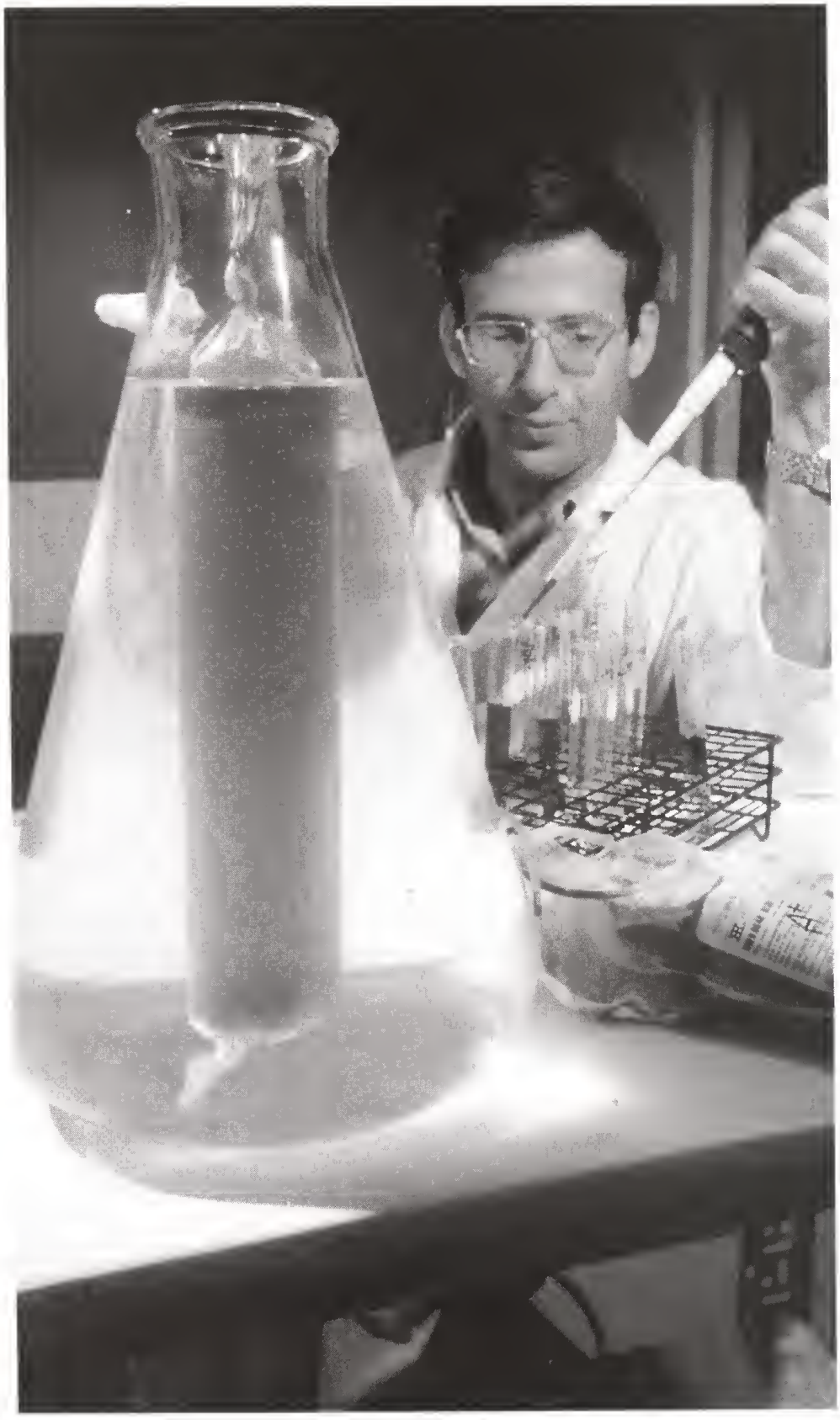
The search for a substance to replace whole blood for transfusions has been underway since the late 1960s.

The hunt for a substance to replace whole blood in transfusions has been underway since the late 1960s. The search has so far been unsuccessful, but research continues because success would eliminate several major problems in using fresh blood. These problems include a supply shortage in the face of increasing demand, the short shelf life of "whole blood" even under refrigeration, transmission of hepatitis, the AIDS virus, and other viral diseases, and the need for careful blood typing.

The primary job of artificial blood is to duplicate the oxygen-carrying function of hemoglobin. Hemoglobin is the iron-containing protein within the red cells of natural blood. Researchers and manufacturers seeking to create artificial blood have concentrated on two things: so-called "white blood" using fluorocarbons, and "red blood" made from modified hemoglobin.

White Blood

Fluorocarbons are organic molecules that are able to dissolve large



In recent years, research into a successful artificial blood formula has been of great importance to many biomedical research companies.

amounts of oxygen. Their potential value was dramatically demonstrated in 1966 by American physician Leland C. Clark, Jr., of the University of Cincinnati. He dropped a live mouse into a beaker full of a liquid fluorocarbon. The mouse was held completely immersed in the liquid by a weight on its tail but continued to breathe. The oxygen dissolved in the liquid is what made this possible.

Early fluorocarbons could not be used in human medicine because they concentrated in the liver and spleen. Ryoichi Naito, a chemist at the Japanese pharmaceutical firm of Green Cross, found he could overcome this problem by mixing perfluorodecalin with the fluorocarbon perfluoropropylamine. The result was a milky white solution called Fluosol-DA. In 1989 Fluosol was approved by the U.S. Food and Drug Administration (FDA) for use during **balloon angioplasty.**. During the time the inflated balloon cuts off blood supply to some tissues, injected Fluosol can carry oxygen to the deprived tissue cells. Animal studies hold promise that Fluosol can be used to carry oxygen to tissues in other cases of blood circulation blockage.

Red blood

A different approach to blood substitution has centered on hemoglobin isolated from the red blood cell. Use of free hemoglobin was suggested back in the nineteenth century, but modern researchers several decades ago discovered that such use had several severe problems. Outside the red blood cell, hemoglobin holds on too tightly to oxygen and does not release enough to the tissue cells. Free hemoglobin also breaks down into two halves that are filtered out by the kidneys, which often causes severe damage.

To eliminate these difficulties, researchers have worked on various ways of modifying hemoglobin. One approach has been to chemically link the hemoglobin subunits together. The linked subunits form a bigger molecule (a polymer) that will not break down. Although researchers were concerned that the giant molecules could damage body organs, animal tests were encouraging.

Clinical Trials

Surgeon Gerald Moss of the University of Chicago licensed his technique for multi-molecule linkage to Northfield Laboratories of Illinois. In 1987 Northfield began clinical trials of the modified hemoglobin in humans. The first round of tests were successful. During the second round in 1989 several trauma patients suffered allergic reactions to the hemoglobin product. This prompted an FDA advisory committee investigation. The investigators learned of a German trial conducted by physician Kon-

rad Messmer at Heidelberg University in the early 1980s in which the two volunteers suffered kidney failure after receiving a modified hemoglobin product. The FDA concluded that many organs of the body could be damaged by hemoglobin-based blood substitutes. The agency abruptly halted Northfield's human trials.

English biochemist Max Perutz discovered hemoglobin's atomic structure in 1960. Somatogen Incorporated of Boulder, Colorado, used this knowledge to produce a genetically engineered, modified hemoglobin that gave up its oxygen more easily and did not break down quickly. Somatogen produced its hemoglobin in yeast or bacteria rather than human or animal substances. The company sought FDA approval for human testing in the early 1990s.

Biopure of Boston began working with modified hemoglobin from cows in 1984 and began human trials of its product in Guatemala in 1990. DNX, a biotechnology company in Princeton, New Jersey, announced in 1991 that it had produced genetically-engineered pigs that made normal human hemoglobin. Some components of plasma, too, could be synthesized by the early 1990s. Genentech of California produced a plasma that promotes coagulation in hemophiliacs.

All these approaches hold promise for artificial blood. Researchers still remain uncertain about the cause of the toxic side effects produced by hemoglobin blood substitutes. They are not sure whether the side effects are due to impurities in the products or to the body's reaction to free hemoglobin.

[*See also* **Angioplasty, balloon; Blood transfusion**]

Artificial blood vessels

Artificial blood vessels are tubes made from synthetic (chemically produced) materials to restore blood circulation. During World War I (1914-1918) French-American surgeon Alexis Carrel (1873-1944) perfected a procedure for sewing the ends of blood vessels together. This achievement that won him the 1912 Nobel Prize in medicine. Carrel also made artificial blood vessels with tubes of glass and aluminum.

The most successful artificial blood vessels in use today come from surgical techniques developed in the 1940s and 1950s. To replace damaged or diseased arteries or veins, surgeons initially transplanted arteries or veins from donors, but these transplants frequently failed. In some cases the donor arteries were rejected by the recipient, while in other cases the ves-

sels developed arteriosclerosis ("hardening of the arteries"). Transplanting vessels from the patient's own body was problematic because two surgeries were required, one to harvest the needed vessel and a second to transplant it. Furthermore, many patients with circulation problems had no suitable vessels that could be transplanted.

To overcome these problems, researchers began to experiment with synthetic blood vessel materials such as polyethylene (a soft and waxy plastic) and siliconized rubber (rubber formed with silicone). These synthetic fabrics showed the most promise.

Synthetic Materials Outperform Natural Ones

A porous material called vinyon, which had been tried on dogs, was first used by A. B. Voorhees on humans in 1953. A variety of synthetic fabrics were subsequently used in experiments; of these, the plastic Teflon and synthetic fiber Dacron proved to work best. Blood vessels made from these synthetics are not rejected by the body's immune system, and the materials are easily available and extremely durable.

While large Dacron blood vessels work very well, small ones have a tendency to become blocked by clots. Researchers are working on ways to make the interior walls of these small synthetic vessels smoother, thus preventing clot formation.

Hybrid Vessels

In the early 1980s chemist Donald Lyman of the University of Utah (Salt Lake City) synthesized a polymer (a plastic formed by long chains of carbon molecules) that had two advantages. Due to a high attraction for albumin (the protein in blood serum), Lyman's polymer reduced clot formation. The polymer also exhibited more elasticity (stretchiness), thereby reducing strain at the site where the natural and artificial vessels were surgically joined. Research Industries of Salt Lake City began testing Lyman's vessels on humans in 1988.

Surgeon David Annis of the University of Liverpool (England) produced a similar flexible, smooth-walled plastic vessel and also began human trials in the late 1980s. In 1990 Organogenesis (a bio-research company) of Cambridge, Massachusetts, began animal testing of its living blood vessel equivalent, which is a hybrid (specialized combination) of natural and artificial materials. This artificial vessel features a smooth inner layer grown in the laboratory from human cadaver (dead body) artery cells and tubules strengthened with Dacron mesh. Another approach worked out by Stuart Williams at Jefferson Medical College, Philadelphia, Pennsyl-

vania, uses cells from the patient's own inner blood vessel lining to grow a lining on the inside of Dacron synthetic vessels.

Artificial bone

For years the main source of bone for replacement purposes was cadavers (dead bodies). In fact, the Red Cross maintains a "bone bank" for just this purpose. Recently, physicians have experimented with using metals for bone replacement. Two alloys (mixtures of two or more metals)—titanium and cobalt chromium—have been frequently tested. Because any foreign substance in the body is subject to rejection, scientists are constantly trying to find more acceptable materials.

Specifically, scientists are looking for substances that more closely resemble real bone. Hydroxyapatite is a mineral that makes up about 65 percent of living bone. Attempts to bake natural hydroxyapatite powder into a hard bone substitute have often failed. The high processing temperature needed for baking causes the hydrogen-oxygen mixture to boil off, leaving researchers with a weak ceramic (a material like pottery or tile). Strengthening the ceramic with silica (a hard, glassy mineral) and other elements usually causes a high body rejection rate.

A chemist at the University of Texas named Richard J. Lagow developed a way the synthesize hydroxyapatite. His process created a strong and porous (full of small pores, or holes, through which material may pass) form similar to tooth enamel. When this material is introduced into the body, its porous nature allows blood vessels and cells to enter. The absoption process gradually breaks down the implant and creates pores into which natural bone can grow. In the late 1980s testing began of Lagow's discovery for dental and orthopedic use.

Artificial heart

The heart functions primarily as a pump to keep blood circulating through the body. Because the heart's job is so repetitive, medical researchers have long considered developing a mechanical pump to replace it. In 1935 French surgeon Alexis Carrel (1873-1944) and famed American aviator Charles Lindbergh (1902-1974) designed a perfusion pump. The perfusion pump was designed to work outside of the human body. Its job was to keep

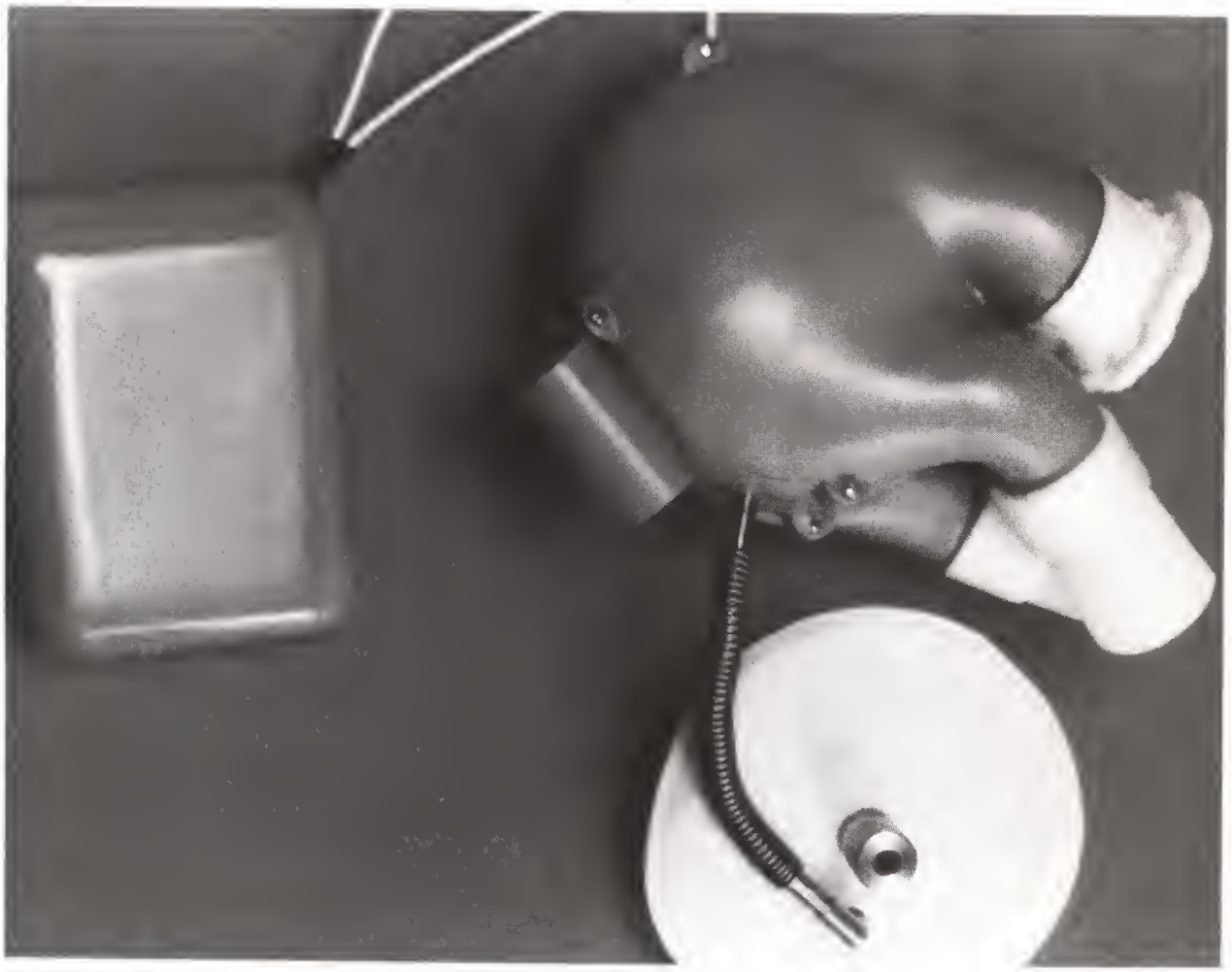
unattached organs, including the heart, alive by circulating blood through them.

Early Developments

The first completely artificial heart (called a "TAH") was implanted in 1957 in a dog at the Cleveland Clinic. Willem Kolff, a Dutch-born surgeon, and T. Akutsu performed the surgery. Kolff later led a medical team at the University of Utah at Salt Lake City in perfecting the artificial heart. In 1964 the National Institutes of Health established an Artificial Heart Program to develop both partial and total artificial heart devices.

Michael DeBakey (1908-) designed and implanted a pneumatically-driven (worked by air pressure) component called a Left Ventricular Assist Device (LVAD) in 1966. The LVAD served the chamber of the heart that pumps blood out into the arteries. Since the majority of severe heart disease is caused by left the ventricle failure, this was a major development.

The first implantation of an artificial heart in a human being ocurrred in 1969 Intended as a temporary measure, its goal was to keep a cardiac patient alive until a heart transplannt could be performed.



Human Experimentation

The first implantation of an artificial heart in a human being was carried out in 1969. Denton Cooley (1920-) and his surgical team at the Texas Heart Institute performed the surgery. The pneumatically driven Dacron-lined plastic heart used in the procedure had been designed by Argentine-born Domingo Liotta. Implanted as a temporary measure, its goal was to keep a cardiac patient alive until a heart transplant could be performed.

It wasn't until 1982 that the first artificial heart implant intended for permanent use was made. A surgical team headed by William DeVries at the University of Utah performed the procedure. Dentist Barney Clark made worldwide headlines when he was given a second chance for life with the Jarvik-7. The Jarvik-7 was designed by American physician Robert Jarvik. The device was a pump made of plastic and titanium powered by compressed air. The compressed air was delivered by a large external (outside) air compressor through two tubes that passed into the body via incisions in the abdomen. Clark survived the surgery for only 112 days.

DeVries then joined the staff at Humana Hospital in Louisville, Kentucky. At Humana he carried out four other Jarvik-7 implants during 1984 and 1985. Each of these patients also died, including William Schroeder. Schroeder survived 620 days, but suffered a long series of debilitating setbacks during that period. The results of actual permanent implantation of the Jarvik-7 revealed its limitations, including the fact that it caused blood clots to form that traveled to the brain and caused strokes.

Current research focuses on a new generation of electrically-powered artificial hearts. These devices use portable battery packs to transmit power via radio signals. The radio signals pass through unbroken skin to an implanted mechanical heart pump. This provides the patient with mobility and eliminates the need for permanent artificial openings in the body. It also reduces the possibility of infection, a problem that existed with the first air-powered heart. The first of these electric devices was experimentally implanted in a human subject in 1991.

[*See also* **Barnard, Christiaan; Transplant, surgical**]

Artificial heart valve

Researchers set out to design a valve that could be easily implanted, have a low rejection rate, would not promote clot formation, and enjoy long-term durability.

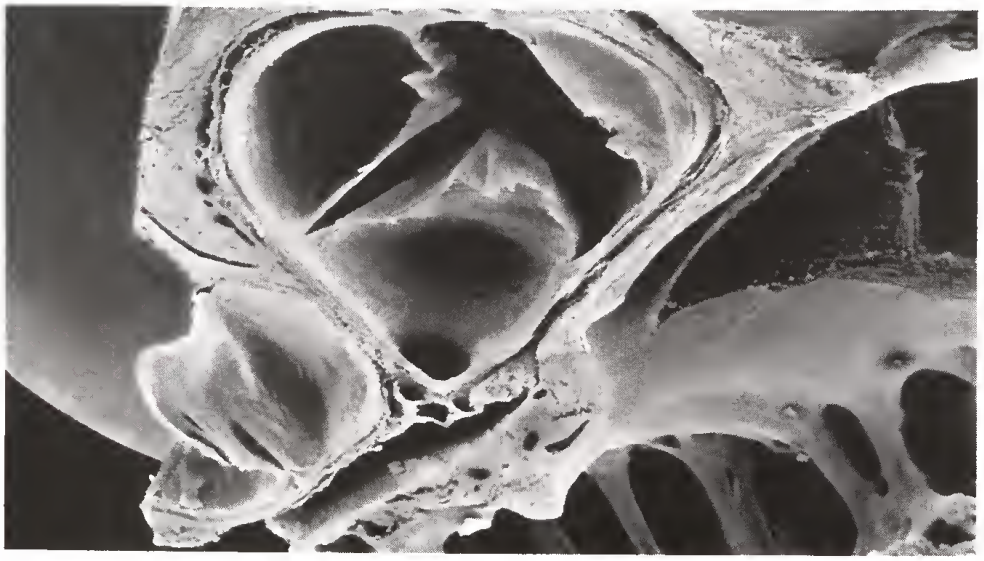
Heart valves are flaps of tissue within the heart. They open and close to allow blood to flow into the correct cardiac areas in the right direction. Blood is supposed to flow from one of the heart's four chambers to the

next. Closing a valve prevents any blood from leaking back. When one of the heart's four valves becomes too diseased or damaged to function properly, blood does not reach the proper area in the right volume. The only effective treatment is valve replacement. Valve replacement was not possible until the advent of **open-heart surgery** in the 1950s. Researchers set out to design a valve that could be easily implanted, have a low rejection rate, would not promote clot formation, and enjoy long-term durability.

American surgeon Charles A. Hufuagel (1916-) inserted a tube-and-float device into a patient's descending aorta in 1952 to prevent aortic backflow. In 1960 Dwight Harken implanted an artificial cardiac aortic valve into a patient. Nina Braunwald replaced a mitral valve with an artificial one shortly after that.

The first completely successful artificial heart valve was designed and implanted in a human patient by surgeons Albert Starr (1926-) and M. L. Edwards in Portland, Oregon in 1961. Their device, the Starr-Edwards valve, is now a standard in the field. The valve is made of a combination of materials and includes a hollow metal ball, an alloy (metal composite) cage, and a Teflon base. Heart valve designers and manufacturers later took advantage of new technologies developed for the space program and included materials like Pyrolite carbon, a strong and durable new substance, in artificial heart valve designs.

There is always the danger of blood clot formation after a valve is implanted. Because of this, patients are required take **anticoagulation medication** for life. An alternative is to use a porcine (pig) aortic valve, which carries a much lower risk of clot formation. Using this valve does



An electron micrograph of a human aortic valve.

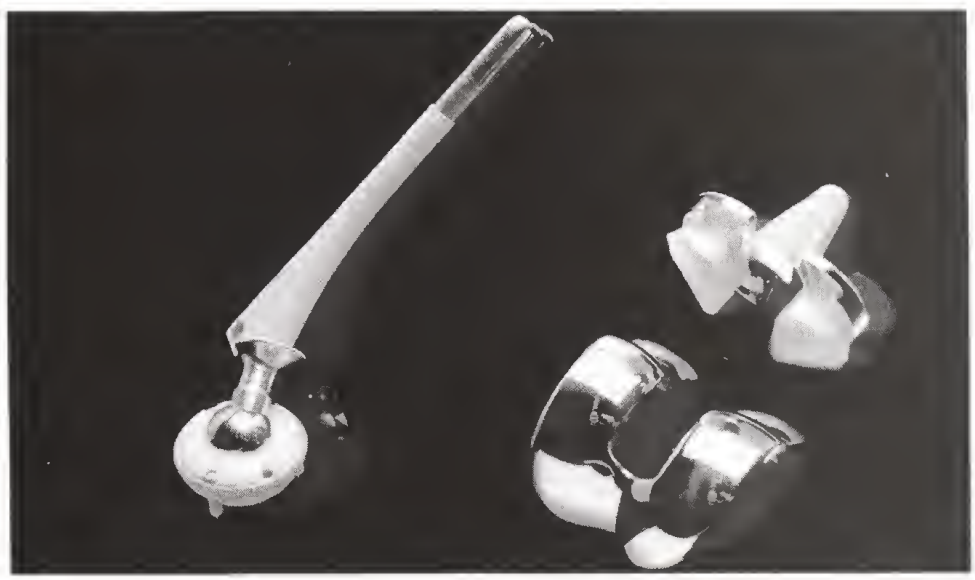
not require anticoagulation medication, but porcine valves do not last as long as mechanical heart valves.

[*See also* **Artificial heart**]

Artificial hip

Artificial limbs have been used since early history to replace arms and legs lost to injury or disease. The Greek historian Herodotus mentioned wooden feet in a writing from 500 B.C. An early Roman mosaic (a large artwork often created from colorful tiles) features a figure with a peg leg (a wooden artificial limb). Medieval knights had simple artificial limbs made to improve their appearance. But artificial limbs are only appendages, things that are attached to the outside of the body. While these limbs must be well-designed and useful, they do not pose the same challenges to surgeons and researchers as artificial joints. Joints are the movable points of the skeleton where two bones come together, such as at the knee, hip, or shoulder. An artificial joint must be implanted (placed) in the body and designed with the same shape and functionality as the connective tissue it replaces.

The study of surgical joint replacement really progressed during the 1950s. Initial testing was done on patients whose joints were degenerated by disease, injury, or malformation (imperfect formation). The replacement procedure was called *total joint arthroplasty.* Hip and knee replacements accounted for 80 to 90 percent of these operations. The first total knee



The materials used in hip replacement surgery must be designed to ensure that a patient's mobility is not seriously hindered.

arthroplasty was performed in 1951; ten years later the first total hip replacement occurred. Shoulder replacements began in the 1960s.

Artificial joints are secured in place either by cement or by a relatively new process called *bone ingrowth.* In the bone ingrowth process, natural bone material (blood vessels and cells) invades the porous (full of very small holes) surface of a synthetic prosthesis (a man-made device, such as a limb, ligament, or bone, that replaces natural material), eventually breaking it down. Complications from replacement surgery include the loosening of the joint's components (parts) and infection, but both problems are fairly uncommon. While a return to normal functionality is not always possible with joint replacement, most patients realize some measure of enhanced mobility and pain relief. Research is ongoing to improve prosthetic materials, surgical techniques, ways of securing the joints, and postoperative mobility.

Artificial kidney

The kidneys perform the vital function of filtering waste materials out of the blood. When the kidneys stop functioning, a person can die quickly from waste buildup. As early as 1861, Scottish chemist Thomas Graham (1748-1843) described a procedure he called dialysis to purify (clean) the blood in case of kidney failure. The blood was spread across a membrane (a thin covering that forms a layer over or between objects and organs) that allowed wastes to pass into a balanced fluid, while replenishing (restoring) substances would pass from the fluid into the blood.

Abel's Studies

Practical application of dialysis was developed by John Jacob Abel, the first professor of pharmacology (the study of drugs) at Johns Hopkins University School of Medicine in Baltimore, Maryland. In 1912 Abel was investigating byproducts in the blood. He needed a device to extract these materials from the blood. With his colleagues Benjamin Turner and Leonard Rowntree, Abel built the first functioning **dialysis machine**. This machine circulated blood through celloidin tubing immersed in a saline (salt)-dextrose (a type of naturally-occurring sugar) solution wrapped around a rotating drum. Urea (a solution found in urine) and other toxins passed out into the solution and oxygen passed into the blood. Abel called

the process vividiffusion, and tested it on rabbits and dogs. Abel, Turner, and Rowntree published their findings in 1914.

The major problem with dialysis in its early days was the tendency of the blood to clot (thicken) while circulating in the machine's tubes. Abel used hirudin, an **anticoagulant** (anti-clotting agent) obtained from leeches, to prevent clotting. Once hirudin was widely available, dialysis became clinically useful. Several researchers developed more advanced dialysis machines during World War II (1939-1945). The need for such machines was urgent because injured soldiers, as well as civilians pulled from the wreckage of bombed buildings, often died from acute kidney failure.

The major problem with dialysis in its early days was the tendency of the blood to clot while circulating in the machine's tubes.

A Functioning Machine

Willem Kolff, a Dutch physician, became interested in saving kidney-failure patients in 1937. Working in Groningen, Holland, Kolff soon put together a crude dialysis machine and worked to refine it. When German troops occupied the Netherlands in 1941, Kolff moved to Kampen. In spite of wartime shortages, he constructed a dialysis machine using cellophane tubing and beer cans. Kolff first used his device on a human patient in March of 1943. Although only one of the 15 patients he treated from 1943 to 1944 survived, Kolff persevered. By the time World War II ended, Kolff had refined his machine. He began to promote its use, bringing dialyzers to The Hague, Amsterdam, and London, England.

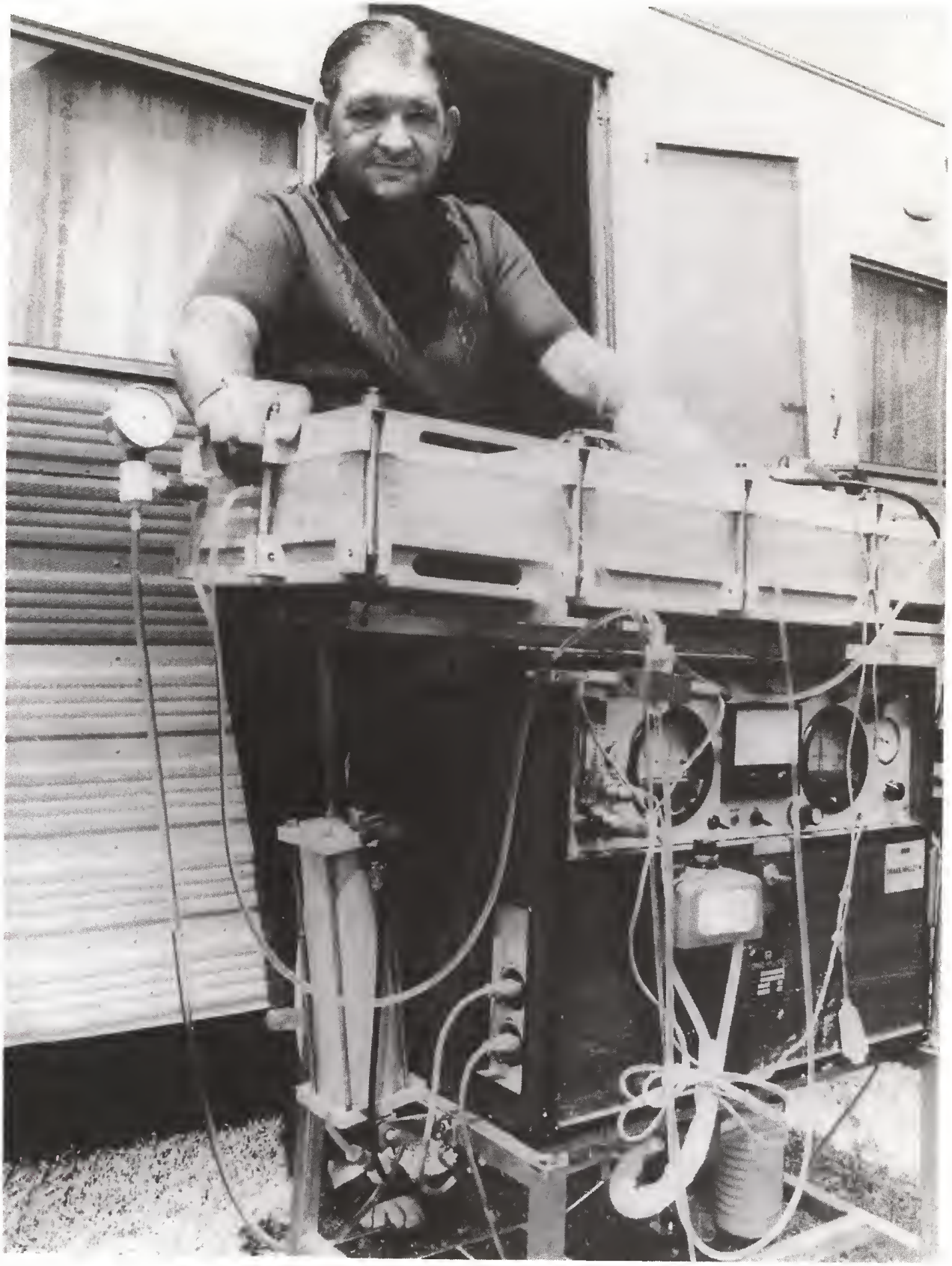
Transplants

In 1947 Kolff traveled to the United States to promote the use of his machine. He gave the blueprints of his latest invention to doctors at the Peter Bent Brigham Hospital (attached to the Harvard Medical School in Boston, Massachusetts) and explained the technique he used. The doctors included John Merrell, Karl Walter, and George Thorn. The trio made kidney dialysis a standard treatment for kidney problems. They also used dialysis to support patients in their pioneering development of kidney transplantation in 1954. Dialysis made the transplanting of kidneys possible by keeping patients alive until their new kidneys started to function. Dialysis also maintained patients whose kidneys had failed until a donated organ became available.

opposite page:
In 1973 Ronald Bell of West Australia took part in a three-month experiment that kept him alive on a mobile kidney machine. Bell spent thirty hours a week hooked up to the device, mostly while sleeping, and still managed to supervise his cattle business.

Long-Term Dialysis

Long-term dialysis was not possible until 1960 because during dialysis, both an artery and a vein had to be punctured (poked). This continuous puncturing eventually lead to vessel deterioration (decay). Dr. Belding Scribner of Seattle, Washington, overcame the puncture problem when he



designed a Teflon and Silastic shunt. The shunt consisted of two parallel tubes with a U-connection that could be inserted into a patient's artery and vein and left in place for months or years. In 1966 the fistula was developed. The fistula is an internal surgical connection of an artery with a vein.

[*See also* **Kidney transplant**]

Artificial ligaments

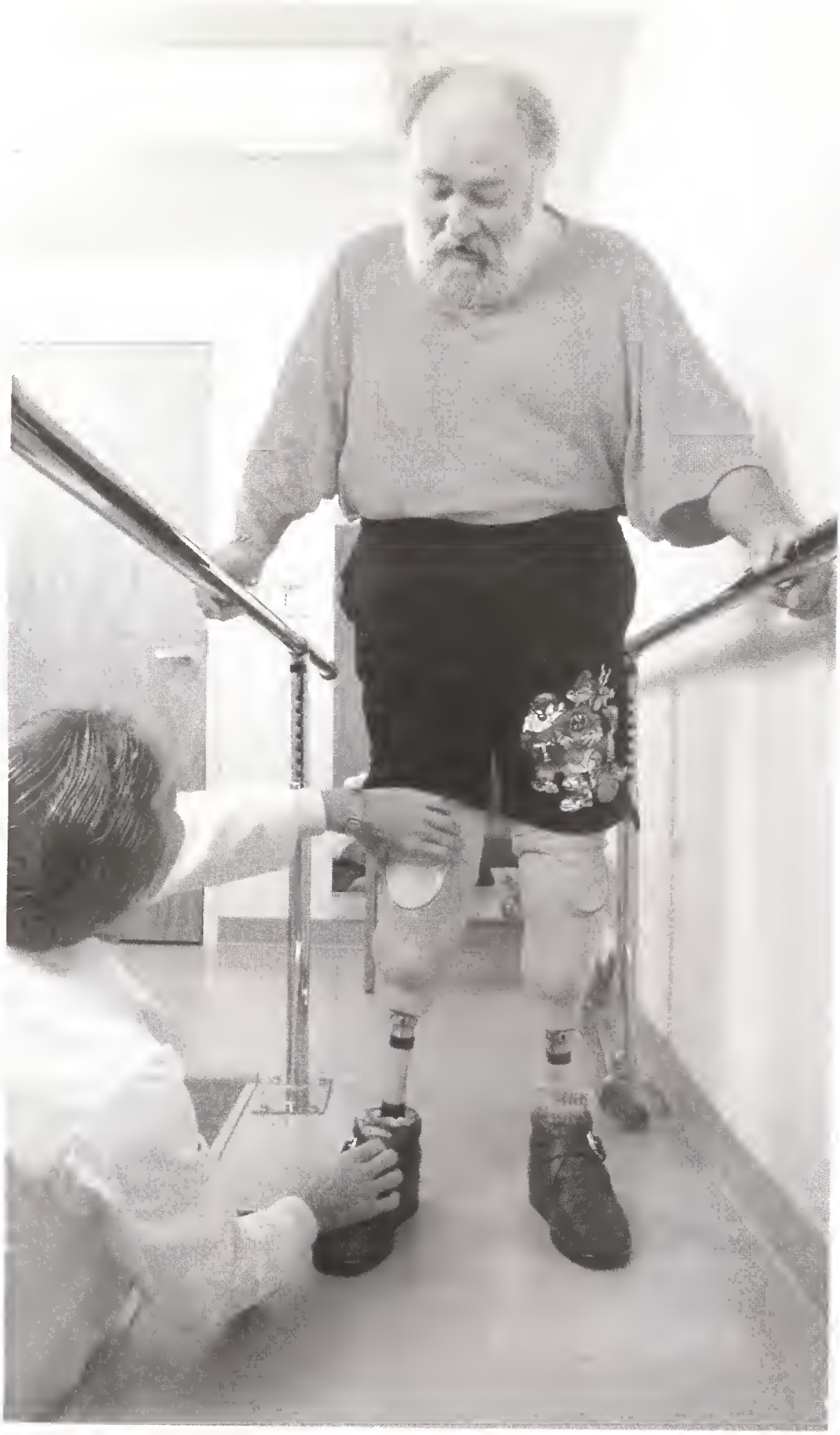
Ligaments are bands of tough, elastic tissue that bind bones together at joints so that they can move. When a ligament is torn, it can either be repaired or replaced. Repair is the first choice, but often a torn ligament heals poorly and must be replaced. Most replacements come from connective tissues in the patient's own body (such as a knee tendon). Rehabilitation and return to full strength can take one to two years.

As anyone who participates in sports or other strenuous activities knows, the knee is very vulnerable to injury. When the knee is subjected to abrupt or progressive stress, one of its four ligaments is likely to tear. Repair or replacement of these ligaments is a major problem. To reduce rehabilitation time and provide greater strength, the W. L. Gore Company developed an artificial ligament made out of Gortex. Gortex is a porous (full of small holes) update of Teflon (a tough material invented in 1969 best known for its use in waterproof materials). The six-inch-long Gortex ligament consists of about 1,000 fibers braided together for strength. The ligament is attached to the bones above and below the knee with stainless steel screws and soon becomes naturally anchored as the bone grows into and through the Gortex.

An artificial knee ligament.

Rehabilitation with the Gortex ligament can be as short as six weeks, and the procedure itself is usually done as outpatient **arthroscopic surgery**. The Food and Drug Administration (FDA) approved use of synthetic ligaments in humans in 1988. The approval, however, was only for patients who had tried and failed with a natural implant.

[*See also* **Artificial hip**]



A man learns to use his artificial limbs and joints with the help of a physical therapist. Advances in replacement surgery allow many patients to enjoy greater mobility and decreased pain.

Artificial limb and joint

A limb or joint lost through accident, disease, or birth defect may be replaced with an artificial limb or joint. Such a replacement is called a "prosthesis," from the Latin word meaning "addition." Crude artificial limbs have been used since the earliest loss of an arm, leg, hand, or foot.

The Modern Era of Artificial Limbs

The modern era of artificial limbs began with the famous French surgeon **Ambroise Paré** (1517-1590; considered the "father of modern surgery"). Paré began his career as a barber-surgeon; in 1536 he became a battlefield surgeon. On the battleground his greatest challenge was developing ways to deal with gunshot wounds. The devastating nature of these wounds meant that soldiers' limbs often had to be amputated. After devising safer, more effective methods of amputation, Paré turned his attention to the design of artificial limbs to replace the ones he had surgically removed.

Paré exercised great ingenuity in his designs, always striving to simulate some degree of natural movement in his mechanical devices. An artificial leg pictured in Paré's *Oeuvres* ("Works") of 1575 featured a movable knee joint controlled by a string and a flexible foot operated with a strong spring. An artificial hand made by Paré had fingers that moved individually by means of tiny internal cogs and levers. When amputating a limb, Paré tried to leave enough stump so that it could be fitted with an artificial limb. Because of Paré's eminence, his ideas and designs for prostheses (plural of the word prosthesis), or artificial limbs, became well known.

Thalidomide Babies

Significant improvements were made in prosthetic design with the birth in the early 1960s of "thalidomide babies." These children were born with a variety of congenital (resulting from problems that occur while a baby grows in the womb) defects, including shortened or misformed limbs. The defects were caused when pregnant women took the drug thalidomide for relief of nausea and vomiting during the early months of a pregnancy. Artificial arms powered by carbon dioxide gas were eventually developed for these children. In the 1960s scientists in the former Soviet Union formed a prosthetic hand controlled by normal nerve impulses from the brain (the messages were picked up by electronic devices in the hand). More recently American scientists developed myoelectric ("myo" means muscle) prostheses. A myoelectric limb moves

when it receives electrical impulses from nerves in the stump of the limb. Modern artificial limbs take advantage of plastics and fiberglass for enhanced strength and comfort.

Joint Replacement Surgery

Joints represent a special challenge for replacement. A joint is the place at which two bones come together, such as at the knee or shoulder. Replacement of joints began in the 1950s. Surgically installing artificial substitutes for joints that have become degenerated by disease, injury, or malformation is called total joint arthroplasty. Replacement of the hip and knee account for 80 to 90 percent of these operations. Other less frequently replaced joints are the shoulder, elbow, and small joints of the hands and fingers. The first total knee arthroplasty was performed in 1951; ten years later the first total hip replacement occurred.

Artificial joints are fastened to the bone either by cement or by a relatively new process called "bone ingrowth" in which the natural bone grows into the porous (full of small holes) surface of the prosthesis. Still, cementing is the favored technique for older patients. Some evidence claims that patients who get bone ingrowth replacement experience longer wear (more time before the artificial joint begins to wear out) than recipients of cemented joints. Artificial joint recipients must watch for signs of infection. Newer surgical techniques, including super-sterile operating rooms, are helping to minimize the risk of infection. Joint replacement does not usually restore normal function completely (for example, the replacement joint is not usually as flexible as the natural joint, and certain types of strenuous activities are limited). Nevertheless, joint replacement usually restores significant mobility and dramatically relieves the pain of problem joints.

Artificial skin

Artificial skin is a synthetic substitute for human skin that can dramatically save the lives of severely burned patients.

Artificial skin is a synthetic (laboratory produced) substitute for human skin that can dramatically save the lives of severely burned patients. Skin, composed of two layers called epidermis (the outer layer) and dermis (the inner layer), is the largest human organ. It covers the entire body, keeping harmful bacteria out and vital fluids in. The epidermis is the outer layer; the dermis is the inner layer that contains the blood vessels, nerves, and hair, oil, and sweat glands.

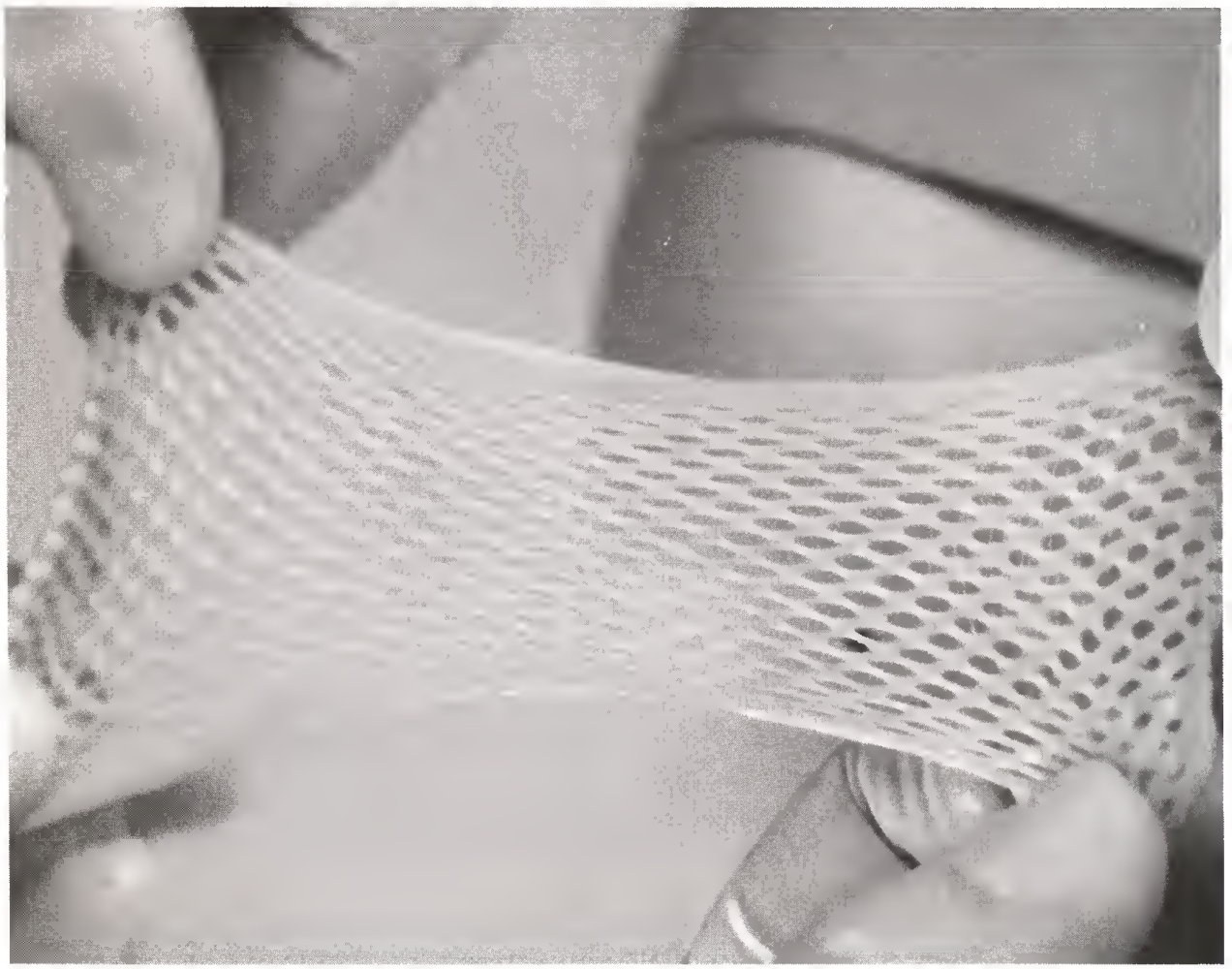
A severe burn leaves the body dangerously vulnerable to infection and dehydration (drying out). Keeping burn patients in sterile (germ free)

rooms can protect against infection, and covering burned areas with grafts (a piece of skin or bone transplanted from one area of the body to another) from the patient's own skin or temporary grafts from other humans or pigs can help save some patients. Still, many burn patients die because their bodies cannot produce large quantities of new skin quickly enough, or because their bodies reject the **skin grafts.**

Burke and Yannas Create Synthetic Skin

The medical community has long been looking for a more dependable alternative. The first synthetic skin was invented by John F. Burke, chief of Trauma Services at Massachusetts General Hospital, and Ioannis V. Yannas, chemistry professor at the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts. Burke had treated many burn victims and realized the need for a human skin replacement. Yannas had been studying collagen, a protein found in human skin. Teaming up during the

New forms of artificial skin have been tested for use on patients with skin disorders, chronic wounds, and certain forms of cancer. Synthetic skin is also being used as a human tissue substitute for laboratory animals in product research.



1970s, the two made a polymer (a chemical compound made of multiple repeating units). Using collagen fibers and a long sugar molecule, they formed a porous (full of small holes) material resembling skin. When placed on the wounds of lab animals, this material seemed to encourage the growth of new skin cells around it.

Burke and Yannas then created a kind of artificial skin using polymers from shark cartilage and collagen from cowhide. This mixture was dried and sterilized to make a thin membrane (a covering through which things can pass) similar to the human dermis layer. Added to the membrane was a protective top layer of silicone that acted like the human epidermis.

Burke and Yannas's experiments with their synthetic skin, called Silastic, showed that it acted like a framework onto which new skin tissue and blood vessels could grow (although these new cells never produced hair follicles or sweat glands, which normally form in the dermis). As the new skin grew, the cowhide and shark substances from the artificial skin broke down and were absorbed by the body. In 1979 Burke and Yannas used their artificial skin on their first patient, a woman whose burns covered over half her body. After peeling away the burned tissue, Burke applied a layer of artificial skin and, where possible, grafted on some of her own unburned skin. Three weeks later, the woman's new skin—the same color as her unburned skin—was growing at an amazingly healthy rate.

Graftskin

At nearby Harvard University, Howard Green was culturing human skin cells under sterile conditions and growing a sheet of human epidermis cells from just a tiny piece of a person's skin. When the cultured skin was placed on a wound area, however, it was rejected by the body's immune system (an internal mechanism for fighting off disease). Green later collaborated with Eugene Bell of MIT, who founded a research group called *Organogenesis*. The research goal at Organogenesis was to make artificial skin that would both include an epidermis layer and resist rejection by the patient's immune system. Organogenesis teams eventually created an extraordinary product called Graftskin, a living skin equivalent made of purified bovine (ox or cow) collagen into which some of the patient's own dermal cells are "seeded" (placed for growth). On top of this layer is an epidermal layer of cultured human skin cells. The Graftskin is formed into four-by-eight inch sheets that can be sutured (sewn) or stapled onto a patient during surgery.

In clinical trials Graftskin grafts have not been rejected by patients' immune systems. Hospital trials have studied burn victims as well as

patients needing skin grafts after cancer surgery, and those with chronic (nonhealing) wounds. After further testing, synthetic skin may become a more common treatment for burns and other serious skin disorders. A welcome side effect of this research is that synthetic skin is a source of human tissue that can also be used to test dermatological (skin) products without lab animals.

Aspirin

Aspirin grew out of a group of drugs called "patent medicines." These medications—some of questionable quality—were very popular from the 1600s to later years of the 1800s. The name "patent" comes from the fact that when a medication was patented (or registered), its formula was owned by the patent holder and no one else could duplicate or sell it. Some early patent medicines had exotic names like "Daffy's Elixer" and "Dr. Hooper's Female Pills." Whatever the name, however, most patent drugs were not terribly effective. Concerns began to grow, especially in the United States, about what was in the patent formulas. Many had very high alcohol levels or were laced with addictive drugs like **opium** and **heroin**. The passage of the Pure Food and Drug Act of 1906 forced all patent medicine makers to list the ingredients of every bottle they sold. An 1938 addition to the law made testing of all medications mandatory; effectiveness tests were added 1968.

Not all patent medicines were phony. Nineteenth-century chemists knew that salicylic acid had pain-relieving qualities, but the acid burned throats and upset stomachs. In 1853 French chemist Charles F. Gerhardt synthesized (formed by bringing together separate parts in a laboratory) a primitive form of acetylsalicylic acid, or aspirin. In 1897 Felix Hoffmann of the Bayer Company found a better method to synthesize the drug and discovered that his version overcame the unpleasant side effects while maintaining the therapeutic effects of the acid. In 1899 Bayer began marketing the new product as Aspirin, a trade name. Bayer lost the use of the trade name in 1919 as part of Germany's concessions to the Allies at the end of World War I (1914-1918), and the name aspirin passed into generic use.

One aspirin-based product, Anacin, was invented by a Wisconsin dentist in 1918. Today, people use aspirin to help with a variety of ills, from headaches to body aches. Aspirin has also been recently tested (and promoted) as a way to control the onset of heart attacks.

Atomic force microscope (AFM)

In recent years, tremendous advances have been made in the field of microscopy (the study of microscopes). The electron microscope (which uses a beam of electrons, or negatively charged particles, to form an enlarged image of an object) is found in most hospitals and medical laboratories. The research behind the electron microscope led to Erwin Wilhem Muller's field ion microscope and the powerful scanning tunneling microscope (STM; developed by Heinrich Rohrer and Gerd Binnig), two of the most powerful optical tools in the world. In 1985 a new microscope was added to this list: the atomic force microscope (AFM). The AFM was invented by Binnig, Christoph Gerber of Zurich, Switzerland, and Calvin Quate (1923-) from California.

How AFM Works

The AFM uses a tiny needle made of diamond, tungsten (a hard, heavy metallic element often used in steel production), or silicon (a nonmetallic chemical element found in most natural things). The AFM scans its subjects by lightly touching them with the needle. In this respect, it uses the subjects like a phonograph record. The AFM's needle reads the bumps on the subject's surface, rising as it hits the peaks and dipping as it traces the valleys. Of course, the topography (map survey) read by the AFM varies by only a few molecules up or down, so a very sensitive device must be used to detect the needle's rising and falling. In the original model, Binnig and Gerber used a STM to sense these movements. Other AFM's use a fine-tuned **laser.**

The AFM has already been used to study the supermicroscopic structures of living cells. American physicist Paul Hansma (1946-) and his colleagues at the University of California, Santa Barbara, are quickly becoming experts in AFM research. In 1989, this team succeeded in observing the blood-clotting process within blood cells. Hansma's team presented their findings in a thirty-three-minute movie, assembled from AFM pictures taken every ten seconds.

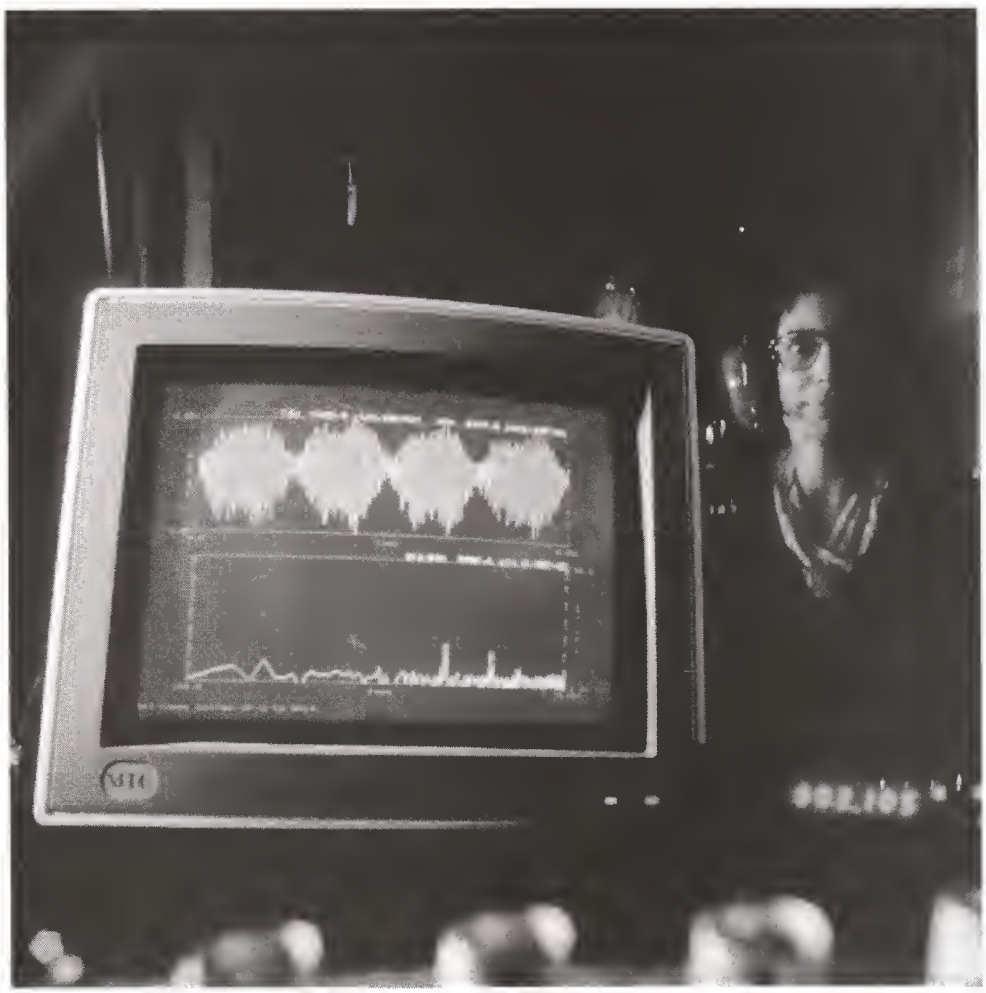
Other scientists are utilizing the AFM's ability to remove samples of cells without harming the cell structure. By adding a bit more force to the scanning needle, the AFM can scrape cells, making it the world's most delicate dissecting (to take apart) tool. Scientists hope to apply this method to the study of living cells, particularly floppy protein cells. The fragility of these cells makes them nearly impossible to view without distortion.

Audiometer

An audiometer is an instrument used to measure how well a person hears. The ear is a complex organ. It receives sound in the form of vibrations that strike the eardrum. These vibrations move from the eardrum through the bones of the middle ear to the cochlea (a spiral-shaped organ filled with fluid). The vibration sets the fluid in motion and sensory cells along the cochlea's basilar (at the bottom or base of) membrane (a thin covering through which things can pass) send messages of the sound to the brain.

The human ear hears a range of sounds from a 15 decibel whisper to 100 decibels of loud music.

The brain distinguishes many distinct sounds. Pitch (the quality of a tone or sound determined by the frequency of sound waves) or frequency is a measurement of how high or low the sound is. Frequency is measured in units called hertz, or vibrations per second. Each sound also has a degree of loudness which is measured in units called decibels. The human ear hears a range of sounds from a 15 decibel whisper to 100 decibels of loud



Audiometers test hearing by exposing patients to a range of sounds at different pitches and decibel levels

music. Sounds of over 140 decibels, such as those made by a jet aircraft, can damage hearing.

The Audiometer Test

An audiometer consists of four parts. These parts are the oscillator (used to change the frequency of sounds heard), an audio amplifier, an attenuator (used to control volume loudness), and a pair of headphones. The person being tested wears the headphones. The amplitude of a tone is slowly increased until the person hears the sound. The lowest decibel level at which a sound is heard is called the threshold. The oscillator is used to change pitch so a range of sounds can be tested. When manufacturing audiometers and performing audiometer testing, care is taken to eliminate background noise.

The result of a hearing test using an audiometer is called an audiogram. The audiogram is a graph that shows the lowest decibel level at which each frequency is heard. The graph gives a profile of the person's threshold of hearing. It compares the profile to a line representing normal hearing in order to detect hearing loss. Using the audiometer, frequency is varied from 64 hertz to over 8,000 hertz. Amplitude can be varied in five decibel increments. In addition to pure tones, speech sounds are sometimes used as test signals. Hearing is considered good if every tone sounded between 64 and 8,192 hertz is heard at a volume of 20 decibels. Hearing loss is generally greatest at the high frequencies. This seems to occur in many people over fifty.

Békésy's Invention

The pure-tone audiometer was invented by Georg von Békésy (1899-1972; winner of the Nobel Prize), a Hungarian-American physicist. His machine was a patient-operated instrument released in 1946. Békésy studied the transmission of sound for a Hungarian telephone company. The testing the telephone lines was routinely carried out and often done with pure tones (tones of one frequency). Békésy listened to everything he heard over the telephone lines—he even listened to the clicks when phones were being connected and disconnected! He started using the clicks as test signals. The clicks themselves were a combination of many pure tones that came along the telephone lines in a single short pulse. Békésy's early experiences helped him study hearing in great detail and arrive at his audiometer design.

Aureomycin

During and shortly following World War II (1939-1945), new "miracle drugs" revolutionized the medical treatment of infections. These new drugs included several types of substances found to have antibacterial (destructive to bacteria) and antiviral (destructive to viruses) properties. One of these classes of drugs was the tetracyclines. Tetracyclines are a family of **antibiotics** similar to **penicillin** that have shown themselves to be both nontoxic (nonpoisonous) and effective against a wide range of infections.

Duggar's Research

Aureomycin, the first of the tetracyclines, was discovered in 1948 by American botanist Benjamin Minge Duggar (1872-1956). Duggar was 76 years old at the time of his discovery. He had graduated from the Mississippi Agricultural and Mechanical College (Mississippi State College) and studied at Alabama's Polytechnic Institute and Harvard University. Duggar later became a professor of botany at the University of Missouri, Washington University, and the Missouri Botanical Garden. He did pioneering research on the tobacco mosaic virus and became widely known for his work with molds and fungi (a group of organisms, such as mushrooms, that lack chlorophyll, roots, stems, or leaves, and reproduce by spores).

Later, as a consultant to the Lederle Division of the American Cyanamid Company, Duggar turned to research on new antibacterial drugs. Although penicillin and **streptomycin** were being widely used to treat bacterial infections, a number of diseases and strains of bacteria were resistant to the treatments. Duggar focused his research on groups of molds found in soil. He tested more than 3,500 strains of molds before he had a success. In 1945 he tested a sample taken from soil at the University of Missouri campus. A golden-hued (colored) substance produced by the mold exhibited antibiotic properties. After extensive testing, he found it to be active against bacilli, staphylococci, and streptococci (all forms of bacteria). Duggar named the substance aureomycin, from the Latin word "aureus," meaning gold, and the Greek word "mykes," meaning fungus.

Aureomycin

Continued testing revealed that aureomycin was effective against 90 percent of bacteria-caused infections. In human trials, the medication was found to be effective against a wide range of infections with minimal side effects. Unlike penicillin and streptomycin, which had to be injected,

aureomycin could be taken orally (by mouth). Aureomycin was also effective in treating diseases that did not respond to other antibiotics, such as trachoma, parrot fever, typhus, chlamydias, and mycoplasmas. It was also active against Rocky Mountain spotted fever, an infection which had spread throughout the United States. Caused by a microorganism called rickettsia and transmitted by a tick, the disease was fatal in one out of every five patients. For a time, aureomycin was added to livestock feed to prevent diseases in animals. This practice has been largely discontinued, however, because it breeds bacteria which are immune to the drugs.

Other tetracyclines include terramycin, achromycin and declomycin. Many medical experts consider tetracyclines to be the least toxic and most effective antibiotics next to penicillin. In certain patients, however, they can cause minor side-effects such as nausea, diarrhea, and tooth discoloration. Because the tetracyclines have been used so widely against a variety of diseases, several strains of bacteria have developed resistance to them. As a result, physicians often prescribe other antibiotics for common urinary tract and respiratory (having to do with the lungs and upper chest) infections.

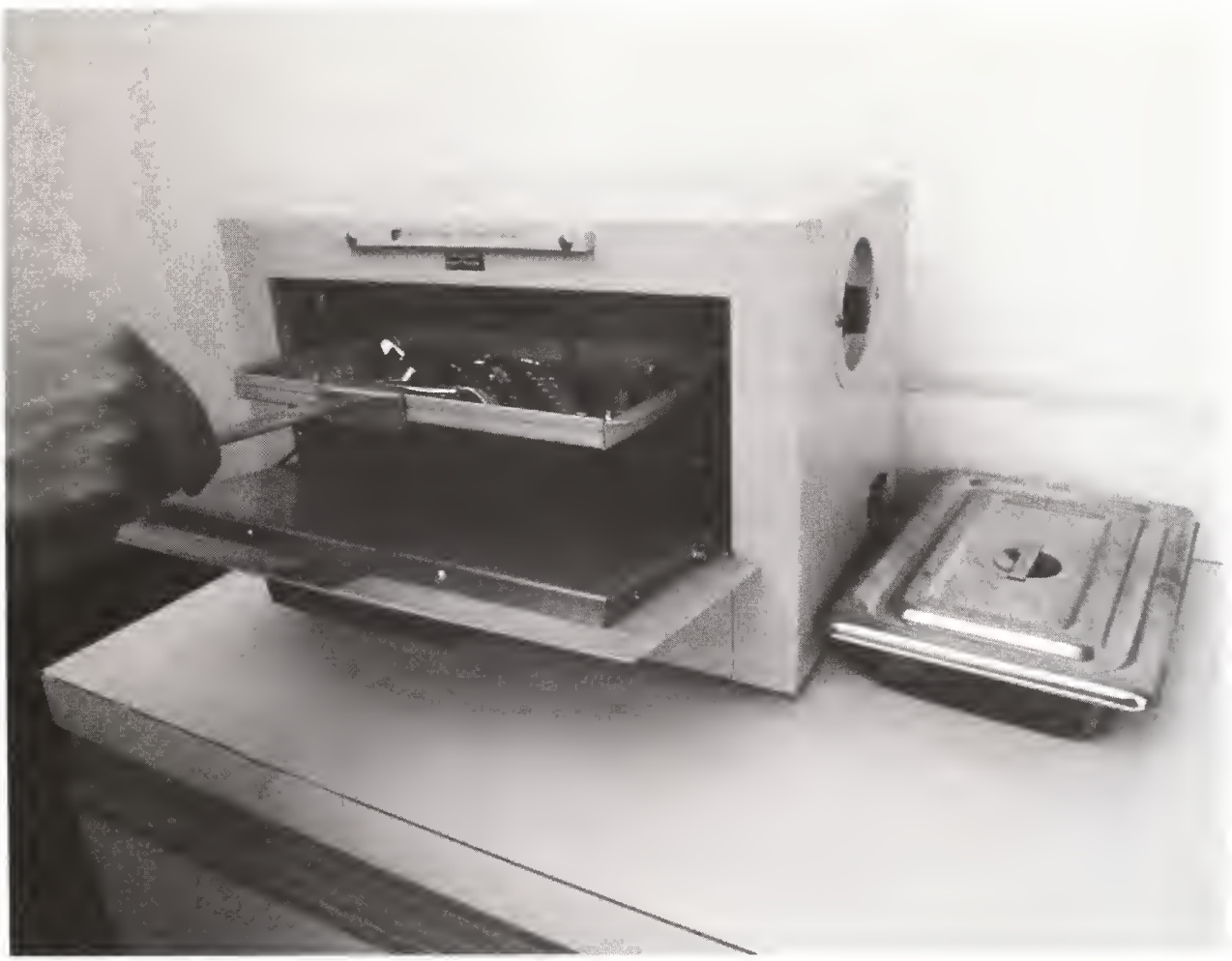
Autoclave

The autoclave is a device used to sterilize (deep clean) medical instruments. It did not start out as a medical instrument. In fact, the autoclave was originally invented and promoted as a method for preparing food by French physician Denis Papin. Papin called his invention a "steam digester." He described his "New Digester" in a 1681 pamphlet, emphasizing the benefits of using the device to process food for easier digestion (the process by which food is broken down for absorption into, or elimination out of the body).

The autoclave was originally invented and promoted as a method for preparing food.

The autoclave is a pressure cooker. A pressure cooker is a container with an airtight lid that traps steam from boiling water. The steam increases the pressure inside the cooker, which raises the water's boiling point. The higher temperature kills bacteria much faster than at lower temperatures. The pressure cooker includes a safety valve to prevent explosion if the steam pressure gets too high.

The scientific basis for sterilization remained a mystery until the work of French chemist **Louis Pasteur** (1822-1895) became widely known and accepted. Pasteur's investigations in the 1850s dealt originally with food, something the autoclave was originally designed to process. In his



Louis Pasteur's search for a solution to the spoilage of beer and wine eventually led to the adoption of the autoclave as a tool for medical instrument sterilization.

search for a solution to the spoilage of wine and beer, Pasteur found that bacteria was killed at 120 degrees Fahrenheit. Applying this to his scientific methods, Pasteur invented the sterile technique of boiling or heating instruments to kill microorganisms. It was Pasteur's efforts that brought about the eventual use of the autoclave as a standard medical tool.

Bandages and dressings

Prehistoric bandages and dressings (materials used to cover a wound) were most likely made from plant materials and strips of animal hide. Fabric bandages were developed later. Early writings from Mesopotamia, Egypt, China, Greece, and Rome describe wound ointments and dressings. Bandages for battle wounds are mentioned in the writings of Homer (c. 900-800 B.C.; author of the *Illiad* and the *Odyssey*), **Hippocrates** (circa 460-377 B.C.; sometimes referred to as the "Father of Medicine"), and the Bible. Ancient Egyptian embalmers (those who treated dead bodies to prevent decay) were highly skilled in the art of bandaging. The great French surgeon **Ambroise Paré** (1510-1590) modernized the treatment of wounds, which were often cauterized (blistered or burned) before they were bandaged. Paré noticed that wounds healed faster when they were not cauterized, so he abandoned the practice in favor of ointments covered with carefully applied bandages. Three hundred years later, English surgeon **Joseph Lister** (1827-1912) pioneered the use of bandages and dressings that he had soaked in carbolic acid as an antiseptic (a substance that stops the growth of the microorganisms that cause infection).

Adhesive plasters, which later evolved into today's adhesive bandages, were mentioned in an 1830 Philadelphia, Pennsylvania, medical journal. Plasters were patented in 1845 by Drs. William Shecut and Horace Day of New Jersey and marketed as "Allcock's Porous Plaster" by Dr. Thomas Allcock. In 1882 German pharmacist Paul Beiersdorf patented a plaster-covered bandage called Hansaplast.

The Modern Bandage

The adhesive bandage as we know it was the invention of Earl Dickson, an employee of the Johnson & Johnson medical supply company. Dickson's wife was continually cutting and burning herself in the kitchen, and Dickson was repeatedly bandaging her with gauze and surgical tape. Dickson saw that his wife needed a prepared supply of these dressings that she could apply herself, so he began experimenting. He laid out a strip of Johnson & Johnson's surgical tape sticky side up on a table and placed a folded-up gauze pad in the middle of the tape. To keep the gauze clean and the tape sticky, Dickson covered the strip with crinoline. Mrs. Dickson appreciated her husband's invention, and so did Dickson's coworkers and bosses. Johnson & Johnson quickly put the bandages on the market, and in 1920 they became Band-Aids (a name suggested by a Johnson & Johnson mill superintendent, W. Johnson Kenyon).

The adhesive bandage as we know it was invented by Earl Dickson, an employee of the Johnson & Johnson medical supply company.

Manufacturers have offered bandages with various adhesives to meet different needs. Some people are allergic to particular adhesives or bandage materials, some need bandages to adhere when wet, while others need a bandage that is removable and reusable. A recent product called Fabrifoam was created by Applied Technology International Limited. Fabrifoam combines polymers, fabric, and foam to create a medical wrap that is being adopted by professional and college athletes. Performing better than the widely used Ace bandage, Fabrifoam breathes, grips better, holds its elasticity longer, is washable, and represents the next development in compression and treatment for soft tissue injuries.

[*See also* **Adhesives and adhesive tape**]

Today's disposable bandages come in many forms and sizes. Some bandage companies have tried using bright colors and cartoon characters to make their product more appealing to young consumers.

Barbiturates

Barbiturate is the name given to a drug made from barbituric acid, a combination of urea (a compound found in urine and other body fluids) and malonic acid. Barbiturates work by depressing (slowing down) the activity of nerves, muscles, heart tissue, and the brain. They are part of a class of drugs called the sedative-hypnotics, which can alter a person's mood and are generally prescribed for relaxation and sleep. Barbiturates act on the central nervous system and can produce effects ranging from mild sedation to coma (prolonged unconsciousness), depending upon the dosage given. If used improperly, barbiturates can even cause death. Barbiturates are not used for medical purposes as often as they once were. In many cases they have been replaced by the more effective and safer sedative-hypnotics called benzodiazepines (such as Valium and Librium). These tranquilizers are also addictive, however, and in some cases have become subject to abuse.

Barbiturate Hazards

Barbiturates can impair a person's ability to think rationally and to reason. They are is highly physically addictive (habit-forming). A person abusing barbiturates may exhibit symptoms similar to drunkenness, including loss of inhibition, loud or violent behavior, lack of muscle coordination, and depression. Withdrawal from barbiturate addiction can produce severe side effects. The addicted person may shake, be unable to sleep, feel anxious, and sometimes experience convulsions and delirium (a state of extreme mental excitement). Death can occur if a person stops taking barbiturates suddenly instead of gradually. If combined with alcohol, barbiturates can be particularly deadly.

Developing Barbiturates

The first barbituric acid was prepared in 1864 by Adolf von Baeyer. His student, organic chemist Emil Fischer, worked with physiologist Joseph von Mering to introduce the first barbiturate derivative (something copied or adapted from existing material) for use as a sedative (a substance that reduces feelings of stress or excitement) in 1903. Fischer and von Mering produced 5.5 diethylbarbituric acid, a hypnotic (a substance that produces a sleep-like state) and sedative known by the trade names Barbital, Veronal, and Dorminal. By 1912 a phenylethyl derivative was developed and commercially introduced as Phenobarbital and Luminal. Since then, more than 2,500 barbiturates have been created. About 50 of these synthetic derivatives have been marketed.

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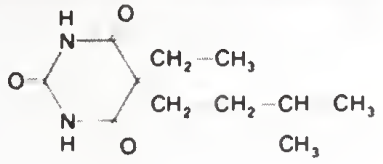
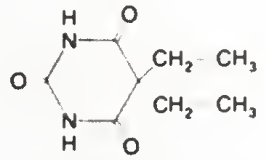
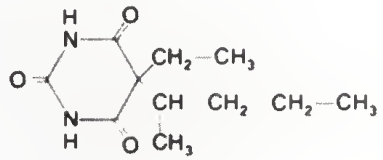
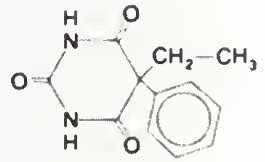
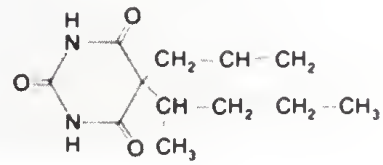
Barbiturate Use

Doctors often prescribe barbiturates to help people relax during times of great stress or to help patients suffering from anxiety disorders. Because of possible side effects, barbiturates are usually given on a short-term basis, and the patient is closely monitored. Short-acting barbiturates such as thiopental are injected as general **anesthesia** before surgery. Pentobarbital and secobarbital are the barbiturates used most often to relax patients before surgery. A long-acting barbiturate, phenobarbital, is prescribed with other medicines to prevent epileptic seizures. Secobarbital was used as a medication to treat anxiety before tranquilizers were developed; it is still used for the short-term treatment of insomnia (the inability to sleep).

Barbiturates are not effective as painkillers until the dosage produces unconsciousness (they can even heighten a patient's sense of pain up to that point). Barbiturate-induced (caused) sleep is characterized by slow brain wave activity. It prevents a person from entering the deepest and most

Chemical name	Trade name	Street name	Chemical structure
Amobarbital	Amytal	Blue heavens	
Barbital	Veronal	Barbs	
Pentobarbital	Nembutal	Nembies, yellow jackets	
Phenobarbital	Luminal	Goofballs	
Secobarbital	Seconal	Red devils, red birds	

A chart of various barbiturate drugs and their chemical compositions.

restful stage of sleep, known as REM (rapid-eye-movement). People are sternly warned not to drink alcohol while taking barbiturates, because mixing these two substances can prove fatal. Alcohol itself is a depressant (something that lowers the rate of body functions). Combining alcohol with a barbiturate can depress the nervous system to such an extent that it ceases functioning altogether.

[*See also* **Tranquilizers**]

Barium

Pure barium is rarely used outside the laboratory. Barium compounds are found primarily in two ores (minerals from which valuable substances, like metal, can be removed). The first ore is barite and the second is witherite. Barite contains a sulfate (a salt of sulfuric acid) compound while witherite contains barium carbonate (a salt of carbonic acid). While barium and all of its soluble (dissolvable) compounds are poisonous, barium sulfate is used in medical procedures because it will not dissolve in water or other body fluids.

Barium sulfate is used in medical procedures because it does not dissolve in water or other body fluids.

Like other metals, barium is a good conductor of heat and electricity. It is silver and white in color and relatively malleable (flexible). Chemically, it resembles **calcium** and strontium, fellow members of the alkaline-earth family of metals. Barium gets its name from the Greek word for barys, which means "heavy."

During the 1700s, chemists thought that barium oxide and calcium oxide were the same substance. In 1774, Carl Wilhelm Scheele showed that barium oxide is a distinct compound. After electric batteries were invented in the 1800s, chemists began using electric currents to break compounds apart. **Humphry Davy,** who pioneered this technique, later called electrolysis, discovered barium in 1808. Davy produced barium for the first time by passing an electric current through molten barium hydroxide. He also used electrolysis to isolate potassium, sodium, calcium, magnesium, and strontium.

Barium and Medicine

Barium's many compounds have a number of practical applications. Perhaps the most familiar is the one used in a medical procedure, the barium enema. When doctors need to examine a patient's digestive system, a mixture containing barium sulfate is used to coat the inner lining of the intestines. Similarly, to enhance examination of the stomach and esophagus, the patient drinks a chalky barium sulfate liquid. When the patient is X-rayed, the barium coating inside the digestive tract absorbs a large proportion of the radiation. This highlights the black-and-white contrast of the **X-ray** photograph, so that doctors can better diagnose digestive problems.

Industrial Uses

Barium also has many industrial applications. Although pure barium metal can be used to remove undesirable gases from electronic vacuum tubes, barium's compounds are much more important to industry. Barium sulfate is a component of lithopone, a white pigment used in paints. Barium carbonate is used in the production of optical glass, ceramics, glazed pottery, and specialty glassware. The sulfate is also an ingredient in oildrilling "muds" or slurries that lubricate the drill bit. The bright yellow-green colors in fireworks and flares come from barium nitrate. Motor oil detergents, which keep engines clean, contain barium oxide and barium hydroxide.

Barnard, Christiaan N.

Robert K. Jarvik's experiments with artificial heart transplants followed Christiaan Barnard's (1922-) pioneering work in human heart transplantation. Barnard rose to international prominence when he performed the world's first human heart transplant at Groote Schuur Hospital in Cape Town, South Africa, on December 3, 1967. Fifty-five-year-old Louis Washkansky, recipient of the first transplanted heart—that of a young woman who became brain dead following an auto accident but whose heart was still beating—recovered well enough to sit up in bed and eat steak and eggs. But eighteen days after his surgery he died of double pneumonia. His immune system, suppressed by drugs and radiation so pneumonia would not attack his new heart, had been unable to fight the infection.

The doctor who performed this revolutionary surgery had been interested in transplant procedures for much of his career. Barnard was born and raised in the South African countryside. Known for his excellent aca-

Christiaan Barnard (far left) discusses procedures with two other surgeons before appearing on the CBS television program *Face the Nation*.

demic performance and photographic memory, he graduated from the University of Cape Town medical school in 1946. During his residency training, Barnard studied tubercular meningitis (an inflammation that results from infection). After he transferred to Groote Schuur Hospital (the site of his famous transplant procedure), Barnard became interested in surgery. Eventually, he and his surgeon brother Marius began experimenting with heart transplants using dogs as subjects. By the end of 1967, Barnard felt prepared to try his techniques on a human subject.

Barnard's heart transplant surgery opened a host of ethical questions, which were widely discussed in forums such as newspapers and magazines. The initial enthusiasm for heart transplant surgery faded quickly, not over ethical quandaries, but because heart recipients continued to succumb to infection. Amid criticism that he had rushed too hastily into a risky procedure, Barnard continued to perform and perfect the transplant procedure. As the operation became more routine, more patients survived longer. By 1983 over sixty-three heart transplants had been done at Groote Schuur under Barnard's direction (including a 1974 double-heart transplant, in which Barnard implanted the heart of a ten-year-old girl in the body of a fifty-year-old man without removing the man's diseased heart).

Behring, Emil von

Emil von Behring (1854-1917) made major contributions to the understanding of the body's immune (biological defense) system, discovered the

first successful treatment for tetanus (a dangerous infectious disease caused by bacteria that enters through a wound or opening in the skin), and came to be known as the "Children's Savior" for his success in conquering diphtheria. Behring was born in Hansdorf, Germany, into a family of 12 children. He studied at the University of Berlin, earning his medical degree in 1880. He served several years as a surgeon in the Prussian Army Medical Corps. It was then that he became interested in infection and how substances in the blood fight disease.

In 1889, Behring went to the University of Berlin to work in the laboratory of **Heinrich Koch** (1843-1910; German bacteriologist). Behring made some of his most important discoveries while working there with Japanese bacteriologist **Shibasaburo Kitasato** (1852-1931; first president of the Japanese Medical Association). The two men studied how the blood produces substances that neutralize toxins (invading organisms). Behring called these substances antitoxins (antibodies). Antitoxins or antibodies are the body's soldiers in the fight against a disease-causing organism.

Blood Serum Therapy

One of the largest killers of young children, the bacterial disease diphtheria swept through Western Europe in the late 1800s. It would create tissues in the throat that tended to block the air way, causing the victim to choke to death. Another frequent epidemic of this period was tetanus, also known as "lockjaw". This disease causes severe muscle spasms and is carried by toxins produced by bacteria that live in soil. Behring and Kitasato found that when animals were injected with small amounts of diphtheria toxins, their blood produced antitoxins which would neutralize the invading organisms. These immunized animals would also remain resistant to the disease for long periods of time, and the antitoxin serum extracted (taken) from their blood could be used to treat other animals. Behring and Kitasato called this technique blood serum therapy, and announced their discovery in 1890. Shortly afterward, Behring published another paper in which he applied the same ideas to diphtheria.

Behring became a professor at the University of Halle (Germany) in 1894, and shortly after, at the University of Marburg (Germany). There he established what is known as the Behring Institute and continued one of his other research interests, the fight against tuberculosis. Although Behring was unable to discover a tuberculosis vaccine, he proposed the theory that the disease was spread by infants drinking milk contaminated by tuberculosis bacilli and devised methods to disinfect the milk. He also continued to search for improved treatments for diphtheria. In 1913

Behring introduced a new toxin-antitoxin preparation that gave longer-lasting immunity to the disease.

Behring's vaccines helped to save the lives of millions of injured soldiers in World War I (1914-1918), as well as countless others threatened by tetanus and diphtheria. For his work, Behring received the first Nobel Prize for medicine in 1901. He died in Marburg in 1917.

Biotin

Biotin is a member of the **vitamin B** family. It is water soluble (dissolvable) and an important coenzyme. Biotin is involved in the metabolism (the process in living organisms and cells that breaks down food into nutrients and waste matter) of carbohydrates and in the synthesis (formation) of fatty acids. Like many vitamins, biotin was "discovered" several times by different people and was given a new name by each of its discoverers.

In the 1920s different researchers isolated a growth factor for yeast that some named "bios," and others called "vitamin H". In 1927, biochemist M.A. Boas was the first scientist to demonstrate a requirement for this compound in animals. Boas found that rats who were fed a diet high in raw egg whites soon developed severe skin rashes, lost their fur, and became paralyzed. This syndrome is known as "egg-white injury." Boas also found a substance in liver that could cure this injury. He called the substance "protective factor x." We now know that egg whites contain the protein and avidin, that—unless destroyed by heat—keeps biotin from being absorbed by the body.

Finally, in 1940, Vincent Du Vigneaud, an American biochemist working for a leading pharmaceutical company, realized that biotin was identical both to vitamin H and to "protective factor x." Intrigued by this discovery, Du Vigneaud went on to work out the coenzyme's complicated two-ring structure. Once the structure was known, it became possible for biotin to be synthesized.

Biotin is now known to be present in virtually every food. Moreover, the body can synthesize it from intestinal bacteria. A biotin deficiency, therefore, is extremely rare. It is usually seen in infants born with a genetic disorder and in people who eat large quantities of raw eggs.

[*See also* **Vitamin**]

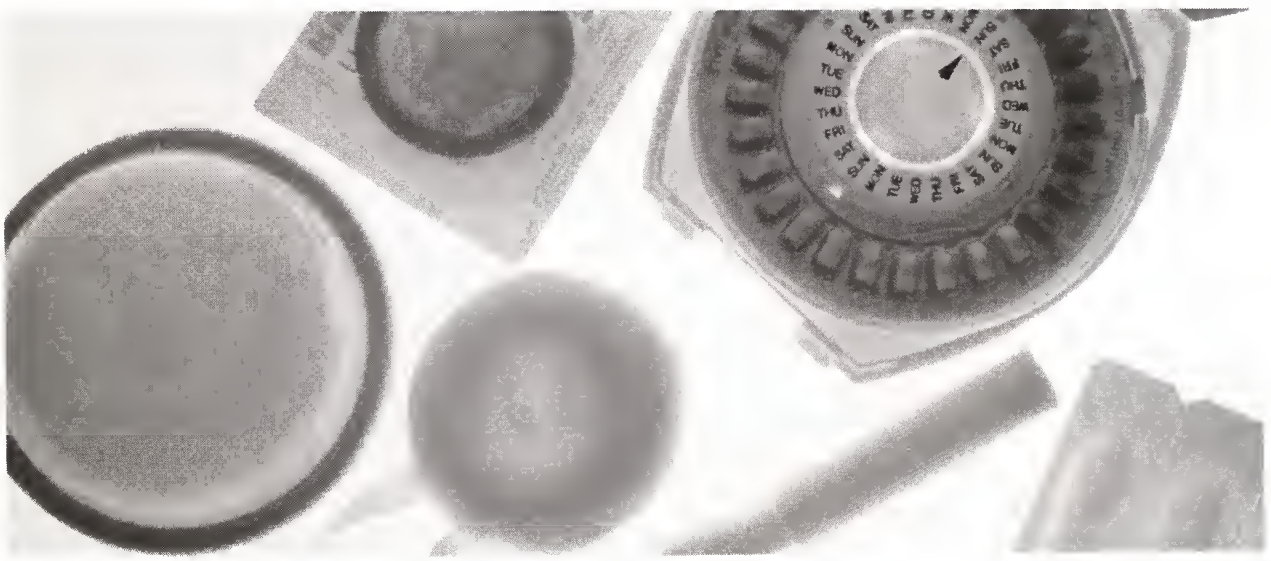
Birth control

Birth control, also known as contraception, is the use of physical barriers, timing, chemicals, or a combination of the three to prevent pregnancy. The vast majority of contraceptive methods are designed for use by women. No method except abstinence (not engaging in sexual intercourse) is guaranteed to be completely effective. Used according to directions, however, most modern birth control methods are safe and effective.

Pregnancy prevention methods have existed in some form throughout history. The methods employed have varied widely, with the religion, culture, and scientific sophistication of each society helping to determine the types of birth control used. In the twentieth century, birth control advocates such as Dr. Marie Stopes (1880-1958) in the United Kingdom and **Margaret Sanger** (1879-1966) in the United States fought prevailing religious and cultural taboos in order to provide information and supplies to anyone who wanted them.

Surgical Birth Control Procedures

Female tubal ligation ("tying the tubes") involves cutting the fallopian tubes (either one of two slender tubes that carry eggs from the ovaries to the uterus), and burning, clipping, or banding the severed ends. Since fertilization of the egg takes place in the fallopian tubes, a tubal ligation prevents pregnancy from occurring. Tubal ligation can usually be performed as outpatient (short-term recovery) surgery and is sometimes performed as an immediate postpartum tubal ligation (in the period of time just after a woman has given birth).



Modern contraceptives offer a range of birth control options. Most methods are designed for use by women, and researchers estimate science is years away from developing an effective "male pill."

Male vasectomy involves severing the vas deferens, the two tubes that transport sperm from the testes to the ejaculatory duct. Since semen thereafter contains no sperm, impregnation cannot occur. A vasectomy is also an outpatient procedure. Some questions have been raised about the procedure's long-term health effects, but the prevailing medical opinion is that vasectomy is unlikely to cause any health problems. Both tubal ligation and vasectomy can be reversed in some cases but generally are considered permanent.

Oral Contraceptives ("The Pill")

Birth control pills contain various amounts of the female hormones estrogen and progesterone that mimic the natural condition of pregnancy, when a woman normally cannot become pregnant. The first contraceptive pill was developed in Massachusetts by endocrinologist **Gregory Pincus** (1903-1967), biologist Min-Chueh Chang (1908-), and physician John Rock (1890-1984). The pill contained progestin, a synthetic progesterone developed in Mexico by American chemist Carl Djerassi (1923-). In 1960 it was approved by the U.S. Food and Drug Administration (FDA) and first became available by prescription under the name Enovid (produced by G.D. Searle & Company.)

Though questions have arisen about their long-term safety and possible links to certain forms of cancer, oral contraceptives are considered appropriate for many women when used under medical supervision. They are the most popular form of contraception and are used by 28 percent of women of childbearing age. Also contributing to their popularity is their high rate of effectiveness.

Long-Lasting Hormonal Contraceptives

Norplant, produced by Wyeth-Ayerst Laboratories, is a device containing a form of progesterone in six tubes the size of matchsticks. These tubes are surgically implanted under the skin. The tubes prevent pregnancy by gradually releasing progesterone over five years. Norplant was approved by the FDA in 1990, though questions have been raised about possible links to cancer, as well as concern about certain side effects, including weight gain, depression, and headaches.

Depo-Provera, produced by the Upjohn Company, is a synthetic form of progesterone that is used in almost 100 countries. One injection works for three months. FDA approval was withheld in the 1970s because of possible links to cancer and osteoporosis. In 1992 the FDA once again began the process of approving Depo-Provera.

Intrauterine Device (IUD)

An intrauterine device (IUD) is placed within the uterus for long-term prevention of pregnancy. It is not known precisely how an IUD prevents conception, but it is believed to produce uterine irritation, causing an inflammatory (fiery, severe) tissue reaction that is toxic (poisonous) to sperm and blastocyst (embryonic tissue).

Modern IUDs date back approximately 100 years. Today's devices, made of plastic, copper, or steel, are formed into loops, coils, and T-shapes. An IUD must be inserted and removed by a physician. Some IUDs have been associated with conditions like perforation (puncture) of the uterus, pelvic inflammatory disease, and even death. A. H. Robins' Dalkon Shield, an IUD design no longer manufactured, is notorious for its high complication rate. At least 20 deaths and thousands of internal injuries have been blamed on its use.

The most successful IUD is the plastic Lippes loop, developed in the 1960s by Dr. Jack Lippes (1924-). The device is straightened and placed in a tube for vaginal insertion into the uterus, where it resumes its loop shape when the tube is removed. Threads attached to the IUD extend into the vagina, so the user can check that the IUD is still in place and has not been expelled. Most contemporary IUDs are variations of the Lippes loop, containing either copper or progesterone.

Condoms

A condom is a latex rubber or lambskin sheath (covering) placed over the erect penis to trap the semen (the fluid containing the sperm) ejaculated (discharged) during sexual intercourse. The condom also helps prevent the spread of venereal disease (sexually transmitted disease, or STD). The condom is the only method of birth control that also decreases the transmission of such diseases as hepatitis, AIDS, and papilloma virus, which is responsible for cervical cancer (cancer of the cervix, the narrow end of the uterus). The practice of using condoms during intercourse dates back to at least the sixteenth century. A condom can be used with or without spermicidal foams or gels.

Diaphragm

Developed in Germany in the late nineteenth century, the diaphragm is a flexible rubber barrier that a woman inserts into the vagina before intercourse. The diaphragm covers the cervix (the narrow end of the uterus that leads into the vagina) to prevent sperm from entering the uterus. The diaphragm is an effective means of birth control when used in combination

Male Contraceptives

For the first time in over 100 years, there is news to report in the field of male contraceptives. Two studies have been using the hormone testosterone to suppress (lower) sperm production. An injectable form of the hormone is featured in World Health Organization (WHO) research, and an oral form is being used by the University of Washington (Seattle) in association with researchers in Bologna, Italy.

Both groups succeeded in lowering sperm production enough to qualify for the WHO's definition of infertility. The WHO study, conducted over two years with men in four continents around the world, showed the injections to be 98.6 percent effective in preventing pregnancy, which is similar to the effectiveness of birth control pills. Sperm counts for the men in both studies returned to normal after the hormones were stopped, proving that the treatment is reversible (the men could later father children).

These studies are exciting because they prove that it is possible to create an effective male contraceptive. The University of Washington study also proves that oral hormones can suppress sperm counts, which was not thought to be possible (researchers believed a concentrated pill form would be toxic). But researchers still predict a long wait—maybe even 50 years—before the male pill will be available.

with a spermicide. Diaphragms come in different sizes, and a woman must be fitted by a birth control expert to get a prescription for the correct size.

Spermicides

Beginning in the 1970s spermicides, chemicals such as nonoxynol-9 that kill sperm, became available in suppositories, foams, creams, jellies, and sponges. Inserted into the vagina before sexual intercourse takes place, spermicides may be used alone or may be combined with condoms and diaphragms for greater effectiveness.

Selective Abstinence

Preventing pregnancy using the rhythm method requires a woman to carefully track her monthly cycle, so she can avoid engaging in intercourse near the time of ovulation. The rhythm method is the only method of birth control accepted by the Roman Catholic church. The temperature

method (developed in 1947) involves monitoring body temperature variations during the monthly cycle. Temperature falls below normal in the weeks before ovulation, drops further during ovulation, and then rises above normal until menstruation. Monitoring variations in the quality and quantity of vaginal secretions can also help pinpoint the ovulation time. The calendar method assumes that ovulation consistently occurs on the fifteenth day of the monthly cycle, and is subsequently highly ineffective.

[*See also* **Abortion; Hormone; RU 486**]

Blood clot dissolving agent

Blood clots are masses of blood cells that have clumped together because of disease or injury. In cases of damage, blood platelets (roundish disks associated with clotting found in mammal blood) mass (gather together) to stop bleeding. The platelets release clot-promoting chemicals and cause a clot to form.

Blood Clots

A blood clot in a vessel is called a thrombus, and it is called an embolus when part of it detaches and travels through the bloodstream, where it can lodge in a blood vessel and block blood flow. A thrombus can form where the body has been injured, where blood vessels are damaged by arteriosclerosis (hardening and/or narrowing of the arteries), or where blood stagnates (chronic bedrest can cause blood to stagnate, or pool, in one location). The thrombus can then block ever greater portions of the blood vessel. Blood flow can become blocked when a blood vessel gets obstructed by blood clots or other foreign matter in the bloodstream. Foreign matter could include air bubbles, fat globules from a broken bone, or fatty substances accumulating on the inside wall of an artery (arteriosclerosis). As blood flow beyond the clot of blood or foreign matter is reduced or cut off, the part of the body thus deprived of oxygen may become damaged. If the brain becomes damaged, a stroke may result. If the heart muscle becomes damaged, a heart attack may result.

Over half of the cardiovascular (heart and blood vessel)-related deaths in the United States are caused by heart attacks, known as acute myocardial infarctions (MI). Strokes, known as cerebrovascular accidents (CVA), are the third-ranking cause of death in the United States (after heart disease and cancer). A clot that stops blood flow to the brain causes 80 percent of all strokes.

New Medicines Dissolve Clots

Blood clot dissolving agent

Many strategies have been developed to prevent these deposits from forming in patients who are prone to them. One approach is to use **anticoagulants** (substances that prevent the blood-clotting factors in the blood from becoming active). Anticoagulants—including aspirin, warfarin, and heparin—thin the blood (reduce the stickiness of blood), which helps prevent clots from forming in the first place.

Until recently, however, there were very few therapies that were able to break down clots that had already formed. Scientists have now developed several substances that can reduce existing clots. These new treatments were first used for heart attack patients, and have recently being used to treat stroke victims.

This process of dissolving blood clots that already exist is called thrombolysis. Three groups of thrombolytic agents are available, including enzymes, which act directly upon the fibrin strands within the clot, plasma activator agents, which increase plasma activator activity, and plasminogen activators, such as streptokinase, urokinase, and tissue plasminogen. All these drugs digest clots by increasing the amount of plasmin (plasmin dissolves clots) in the blood. To produce plasmin, the substance plasminogen must first be activated. Plasminogen is converted into plasmin by certain enzymes known as plasminogen activators.

Streptokinase has been used since about 1960. Researchers use streptococci bacteria to produce this drug. Although streptokinase is the least expensive activator, some negative side effects, such as immune responses, have been experienced by patients. Urokinase is found naturally in humans, especially in the urine. Thus, no negative immune response is associated with its use. This therapy is usually administered in small doses and combined with other drugs, because it is difficult to purify, and therefore rather expensive.

Tissue Plasminogen Activator Aids Heart Attack and Stroke Victims

Tissue plasminogen activator (tPA) is currently the most expensive drug for dissolving blood clots. It is unique because it activates only fibrin-bound plasminogen and thus targets the clot site. tPA in human blood is produced in very small amounts by vascular endothelial cells. Since about 1980, when tPA was first purified from human uterine tissue, it has enjoyed widespread use among American physicians. Lately, researchers have even used **cloning** technology to recombine the genes that encode human tPA. Cloning is transferring the genetic material from one organism into another organism, such as a virus or bacteria, which is called a

host. The host reproduces, new generations of offspring, called clones, that are identical genetically. Scientists have cloned hamster genes to produce tPA in large quantities. This should help make the drug more affordable.

Each of these thrombolytic agents shows great promise in reducing the severity of heart attacks. More recent studies of using tPA for certain stroke victims show significant reduction of brain injury if given within three to six hours of the start of the stroke. This is very exciting, because until now no treatment has served to limit the damage caused by stroke. However, studies are ongoing to define which patients will benefit from tPA, because tPA given to the wrong type of stroke patient could start an episode of severe bleeding.

[*See also* **Gene**]

Blood pressure measuring devices

Modern health care experts know that a patient's blood pressure is a good indicator of how healthy a person is. A high blood pressure reading indicates stress and possible heart problems. The blood pressure device we use today has its roots in seventeenth-century England.

During his studies on blood circulation, William Harvey noted that blood pulsated out of a severed artery as if it were under rhythmic pressure.

William Harvey (1578-1657) did pioneering work on blood circulation in the 1600s. During his studies, Harvey noted that blood pulsated (beat or throbbed) out of a severed artery as if it were under rhythmic pressure. Nearly a century later, Stephen Hales (1677-1761), an English clergyman and physiologist, continued those studies. Hales devised a method to measure the pressure exerted on the blood vessels as blood was pumped through them. He inserted a brass pipe into an animal's blood vessel and used the flexible windpipe of a goose to connect the pipe to a long glass tube. The height to which the animal's blood spurted up into the tube gave a measure of the pressure on the blood.

One of Hales' most dramatic experiments using this simple manometer involved a white mare, tied flat on the ground to a stable door. The glass tube in this instance was 12 feet, 9 inches (3.8m) long, and the horse's blood rose in it to a height of 9 feet, 6 inches (2.9 m). Hales began his blood pressure measurement experimentation around 1706, continued around 1712-1713, and finally reported his technique in his 1733 book *Haemastaticks* ("Blood Facts").

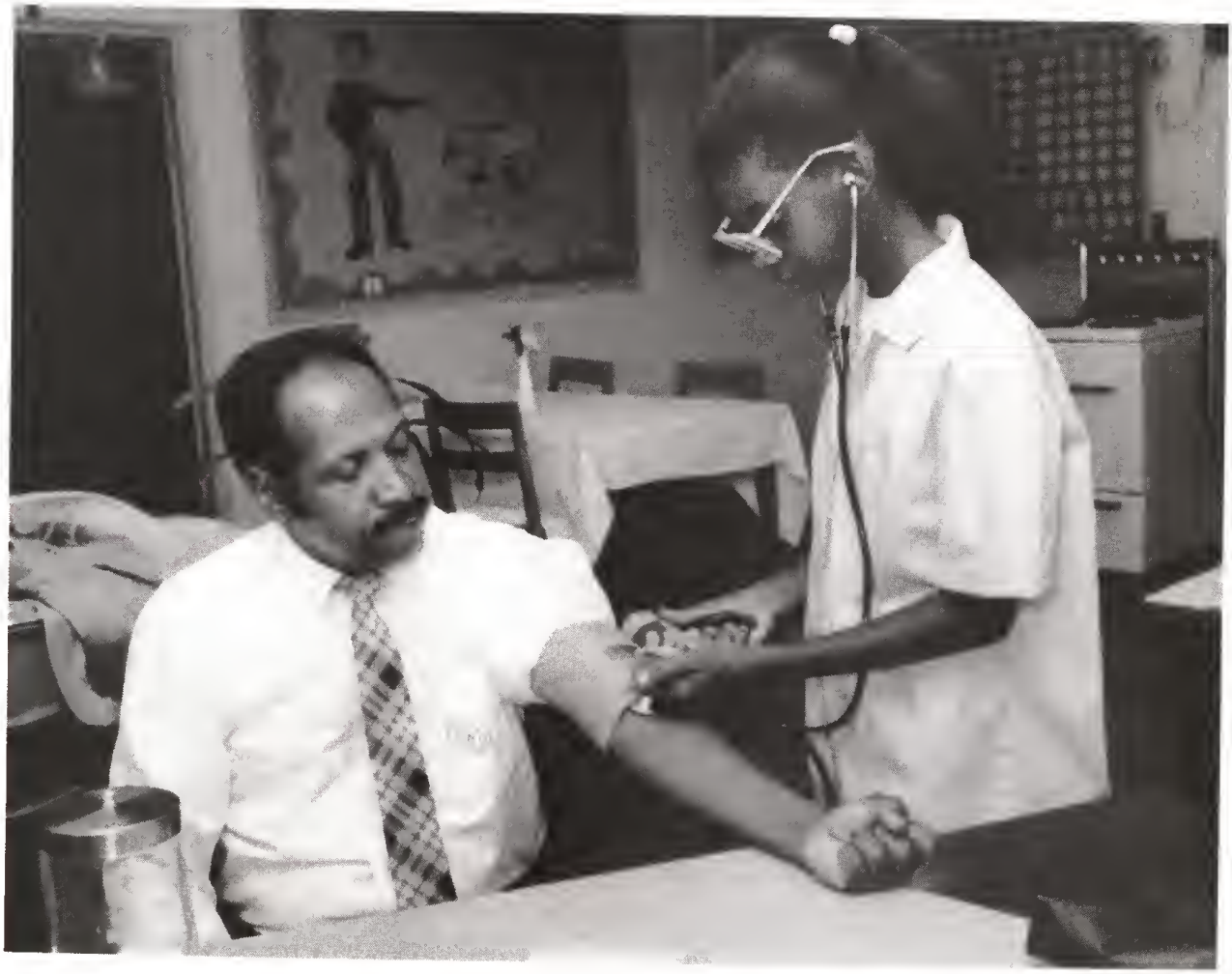
It took another century before the Hales manometer was improved upon. In 1828 French physician Jean Leonard Marie Poiseuille (1797-

1869) replaced the long glass tube with a U-shaped tube filled with mercury. The tube was calibrated in millimeters of mercury to record pressure levels. The German physiologist Karl Friedrich Wilhelm Ludwig modified Poiseuille's manometer in 1847. He added a revolving cylinder and float with a revolving drum on it. By attaching a pen to it, the blood pressure levels could be recorded on this kymograph. In 1863 Etienne-Jules Marey created a better recording machine he called a sphygmograph.

Blood pressure measuring devices

A Practical Device

All of the blood pressure devices developed up to the 1870s required that the blood vessel be penetrated for the pressure to be taken. It took Samuel Siegfried von Basch (1837-1905), a German physician, to come up with the sphygmomanometer in 1876. This device was the first to measure pressure without piercing the skin. His device was replaced in 1896 by a sphygmomanometer made by Italian physician Scipione Riva-Rocci (1863-1937). This device was the prototype of today's standard instrument.



A young girl uses a modern blood pressure measuring instrument. Today, home versions of this device are widely available.

It used an arm band which could be inflated until the blood flow through the arteries could no longer be detected. Air was then released from the band. The blood pressure was measured on a mercury manometer at the moment when the pulse reappeared.

Riva-Rocci's instrument was accurate. The only problem was that it measured only systolic pressure (pressure within the artery when the heart is contracting). Russian physician, Nikolai Korotkoff added the missing element in 1905 when he suggested that a **stethoscope** be used to listen to the blood flow. Heard through the stethoscope, the tapping that begins when air is released from the band is the systolic pressure. The moment the tapping sound disappears is the diastolic pressure (pressure between contractions while the heart is at rest).

Wide clinical use of blood pressure measurement using the sphygmomanometer was promoted by American surgeon Harvey Williams Cushing. Standard readings were soon established and became basic indicators of heart and lung health or problems. Today, home blood pressure devices are widely available and in use, with a mercury tube, a circular needle gauge, or an electronic display to give readings.

Blood transfusion

Blood transfusion is the process of transferring blood from one person's body to another. A severely injured person or one undergoing surgery may need extra blood to replace that which has been lost. If the extra blood is not available, the person can go into shock and die.

Pope Innocent VIII was transfused in April, 1492, with the blood of three young boys. The outcome indicates why transfusion attempts were rare and dangerous: all three boys died.

Folk medicine and ancient practice long considered blood to have beneficial, healing properties. Perhaps the earliest recorded case of blood transfusion was that of Pope Innocent VIII (1432-1492). The Pope was transfused in April 1492 with the blood of three young boys. The outcome indicates why transfusion attempts were rare and dangerous: all three boys died.

After **William Harvey** (1578-1657) explained the mechanism of blood circulation in 1628, interest in transfusion grew. An Italian physician, Giovanni Colle, gave the first concise description of a blood transfusion in 1628. An English clergyman, Francis Potter, seems to have experimented with transfusions in the 1650s. In the 1660s, the Royal Society of London (England) sponsored a series of transfusion trials. This was after Sir Christopher Wren (1632-1723), the famous architect, used

a quill-and-bladder syringe to inject fluid into the vein of a dog. The injection was done to demonstrate a new method of administering medications. Richard Lower (1631-1691) continued the experiments at Oxford University in England and performed the first direct blood transfusion from one dog to another in 1665 by connecting an artery to a vein via a silver tube.

French physician, Jean Baptiste Denis (1643-1704), used Lower's technique in June of 1667 to perform a transfusion from a lamb to an ill human. Several months later, both Denis and Lower transfused blood from a sheep to a man. The promising new technique was abruptly halted in 1668 when one of Denis's transfused patients died. Even though the cause of death was poisoning by the patient's wife, transfusions were banned in France and did not become medically established in England.

In 1818 James Blundell, a physician at Guy's Hospital in London, revived the practice of transfusion by using a **syringe** to inject blood from human donors. At first Blundell transfused only hopeless cases, but in 1829 he used blood transfusion successfully to treat a woman with postpartum hemorrhage. Both Blundell and James N. Aveling improved the apparatus for carrying out transfusions. The technique was widely used during the Franco-Prussian War (1870-1871).

Perhaps most serious of the remaining risks of blood transfusion is the possibility of transmitting disease via the donor's blood. Of special concern is the transmittal of the HIV virus and hepatitis

Typing Blood

Blood transfusion remained a risky procedure. The donor's blood tended to coagulate, and recipients were likely to suffer a fatal transfusion reaction. The discovery of blood groups in 1900 solved the problem of fatal reactions. In 1914 the use of sodium citrate as an **anticoagulant** answered the problem of blood clotting. Austrian-American pathologist Karl Landsteiner (1868-1943) showed the existence of three distinct blood types (groups; the number rose to four in 1902) in an "ABO" system. Antigens in some types reacted adversely to antibodies in other types, causing the clumping of red cells. The clumping could fatally block blood vessels. Landsteiner's findings made it possible to identify donor and recipient blood types and thus avoid the deadly transfusion reaction in most cases. Typing of blood for transfusion began in

1907. Transfusion reaction was more fully overcome in 1940 when Landsteiner and Walter Weiner (1899-) discovered the Rhesus factor (**Rh factor**), which typically causes the antigen/antibody reaction.

The Modern Procedure

At first, blood transfusion was done via direct connection between donor and recipient. George Washington Crile (1864-1943), an American surgeon, developed a standard surgical method of blood transfusion. After surgically exposing a recipient's vein and a donor's artery, a physician clamped shut the vessels and attached a small tube as a conduit between them. When the surgical clamps clamps were opened, blood flowed from donor to recipient. Edward Lindeman took the procedure out of the operating room in 1913 with a simple needle puncture technique. This method also allowed exact measurement of the amounts of blood being transfused. With all these advances in place, blood transfusion spread rapidly and became firmly established during World War I (1914-1918).

Blood Banks

Once blood transfusion was in wide use, storage of donated blood became a problem. The first "blood bank" was set up by Dr. Bernard Fantus in 1937 at Cook County Hospital in Chicago, Illinois. A method of preserving red blood cells for up to 21 days with acid citrate dextrose was developed in the 1940s. African-American surgeon Charles Richard Drew studied in depth a way to preserve and store blood ready for instant use. He discovered that plasma could be processed and reserved for a long time, and transfused without regard to blood type or matching in place of whole blood. Drew established blood banks in England and the United States during World War II (1939-1945). These banks saved thousands of lives by making blood transfusion available to the wounded.

Today, blood transfusion remains a widely used and critical medical procedure. After World War II, methods were developed for separating the various constituents of blood. As a result, in addition to whole blood, a patient may receive "packed" red cells, granulocytes (white cells), platelets, plasma, or plasma components. Both natural and **artificial blood** substitutes are also used. Perhaps most serious of the remaining risks of blood transfusion is the possibility of transmitting disease via the donor's blood. Of special concern is the transmittal of the HIV virus and hepatitis. For this reason, donated blood is carefully screened.

Blue baby operation

Before 1944 babies who were born with cyanosis either died or lived with painful physical defects. Cyanosis is a condition of bluish skin caused by lack of oxygen in the blood. The plight of these "blue babies" aroused the interest of Dr. Helen Taussig of Johns Hopkins Hospital in Baltimore, Maryland. Taussig became head of that hospital's Children's Heart Clinic in the 1930s. After much pioneering fluoroscopy (using a fluorescent screen and **X-ray** transmissions to view internal structures) research, Taussig developed a theory that cyanosis was due to constriction (tightening) of the pulmonary artery. (The pulmonary artery carries oxygen-depleted bluish blood from the heart to the lungs. Once in the lungs, the blood absorbs oxygen and becomes red again). With this information, Taussig visited heart surgeon Robert Gross (1905-) of Boston, Massachusetts. Gross had developed an operation to close babies' blood vessels. Taussig was convinced that a reverse operation should be possible, one that would open a blocked blood vessel.

In 1941 Dr. Alfred Blalock (1899-1964) became chief of surgery at Johns Hopkins. Blalock had an excellent reputation as a vascular surgeon, and had conducted research in blood vessel bypass surgery. Taussig interested Blalock in her theory about cyanosis. Together they experimented on hundreds of dogs to perfect an operation in which a branch of the aorta is joined to the pulmonary artery. This creates a bypass of the defective portion and assures an adequate flow of blood to the lungs. In 1944, Blalock and Taussig performed the first "blue baby operation" on a 15-month-old girl. Two more successful operations followed. A paper by Taussig and Blalock reported the procedure in a 1945 edition of the *Journal of the American Medical Association.*

The operation these two surgeons performed became known as the "Blalock-Taussig Shunt." The procedure was soon widely adopted and saved thousands of babies' lives. Surgeons came to Johns Hopkins from around the world to learn the new procedure, and Blalock traveled abroad to further spread knowledge of the operation. This operative technique is still used today for very young children. It keeps them alive until they are old enough for open-heart surgery. A modified procedure using man-made material for the shunt was first performed in 1963. The Blalock-Taussig procedure was the beginning of the modern era of heart surgery. It paved the way for **open-heart surgery** and surgical correction of many congenital heart defects.

[*See also* **Artificial heart; Angioplasty, balloon; Barnard, Christiaan**]

Bourgeois, Louyse

French midwife Louyse Bourgeois raised her profession to a new level of competence.

Louyse Bourgeois (1563-1636) was the most famous midwife (a person, historically female, who helps other women give birth) of her time. As one of the first educated and medically trained midwives, she raised her profession to a new level of competence and promoted the spread of that competence through her widely read books recounting her observations and experiences.

Bourgeois, a woman of the middle class, acquired some of her medical knowledge from her husband, an army surgeon. She was also fortunate to be one of the first graduates of the new school for midwives at the Hotel Dieu Hospital in Paris, France. At the school, she may have studied under pioneering surgeon **Ambroise Paré** (1510-1590; famous for researching and improving amputation procedures). Bourgeois developed a very large and successful practice, especially among the French aristocracy. She attended the birth of the future King Louis XIII (ruled France from 1610-1643)—reportedly saving the newborn from suffocating—as well as the five other deliveries of Marie de Medici, wife of Henry IV (ruled France from 1553-1610).

Since Bourgeois' popularity rested mostly on successful deliveries, her reputation suffered a bit when she was held responsibile in the death of the queen's daughter-in-law, the Duchesse d'Orleans. The Duchesse died from peritonitis (a bacterial infection) following a delivery in 1627. Despite this setback, Bourgeois remained fairly influential and successful (although she never received the pension King Henry had promised her).

Bourgeois advanced obstetrical (childbirthing) knowledge with her observations about the importance of detachment of the placenta (the bag of fluids that the baby lives in while inside the mother's uterus that is expelled by the mother after birth). If the placenta is not expelled, the mother may hemorrhage (die of uncontrolled bleeding). Bourgeois may have been the first midwife to write books about her specialty, the most important of which was *Observations diverses sur la stérilité* ("Observations on Infertility"), published in 1626.

[*See also* **X-ray**]

Bragg, William Henry & William Lawrence

The team of William Henry (1862-1942; president of the Royal Society; knighted in 1920) and William Lawrence Bragg (1890-1971; knighted in

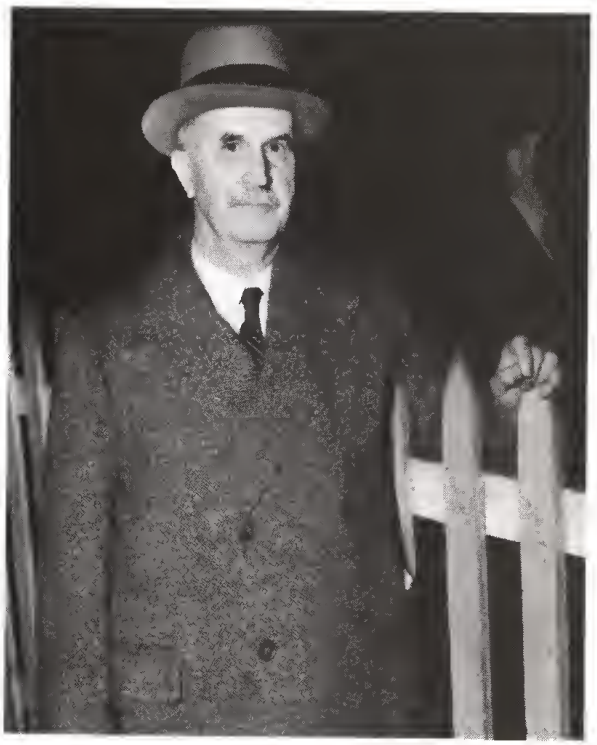
1941) is one of the most scientifically productive in history. The duo succeeded in constructing the first X-ray spectroscope (an optical instrument that breaks up light from any source into a spectrum for study), establishing the science of **X-ray crystallography.** In 1914, the father-and-son pair won the Nobel Prize for physics, the only team ever to be so honored. The win made William Lawrence, at age twenty-five, the youngest Nobel recipient in history.

William Henry

William Henry Bragg was educated on the Isle of Man at King William's College. He entered Cambridge University at age nineteen to study physics under John William Strutt, Lord Rayleigh (1842-1919) and Sir Joseph J. Thomson (1856-1940). After graduation, Bragg took a position at the University of Adelaide (Australia) in 1886. During the next eighteen years, he established a reputation as a great teacher. Bragg published almost no papers, however, and conducted no original research until he was forty-one years old.

The turning point in Bragg's career came in 1906. As co-president of the Australasian Association for the Advancement of Science, he was expected to deliver an address. For his topic, Bragg chose recent breakthroughs in radioactivity. Inspired by the research being done yet recognizing several flaws in the findings, he decided to pursue his own line of inquiry. For the next two years Bragg made contributions to radiation physics, particularly the study of alpha particle emissions.

William Henry Bragg arrives in America to deliver a lecture in front of the American Academy of Science.



Meanwhile, William Lawrence Bragg was walking firmly in his father's footsteps. Recognized as a child prodigy, the younger Bragg entered the University of Adelaide when he was fifteen. He spent most of his time helping with his father's research. William Lawrence was the recipient of Australia's first medical X-ray examination when his father used a home-built X-ray machine to examine his fractured elbow.

In 1909 when the Braggs returned to England, William Henry taught at Leeds University and William Lawrence attended graduate courses at Cambridge. The Braggs eventually became intrigued with Max von Laue's (1879-1960) discovery of X-ray diffraction. Laue had used a crystal to create a diffraction (the break-

ing up of a ray of light into dark and light bands) pattern, proving that X-rays were transverse (crosswise) electromagnetic waves, like those of light. William Lawrence developed a system of equations based upon the theory that crystals were arranged in planes of molecules. Using these equations (now known as "Bragg's Law"), the father and son began a series of experiments that culminated in the invention of the X-ray spectroscope in 1913.

The first application of the X-ray spectroscope was to examine the structure of certain crystals. The Braggs discovered that sodium chloride crystals are not made of molecules at all, but rather patterns of sodium ions and chloride ions. This early experiment also served as the foundation for the science of X-ray crystallography. Crystallography has since become an important tool for chemists and mineralogists and was the key process in the research of DNA (genetic) structure.

In addition to their highly technical research achievements, both Braggs had talent for passing on the wonders of science to the public.

In addition to their highly technical research achievements, both Braggs had talent for passing on the wonders of science to the public. William Henry was a sought-after speaker in Europe, and William Lawrence enjoyed writing science books for children.

[*See also* **X-ray; X-ray machine**]

Breast implants

Breast implants are designed to either enlarge existing breasts, or to reconstruct breasts after surgery. Until very recently, the vast majority of implants were made of silicone (a generic term referring to organic, or living, compounds resistant to heat, water, and many other elements). Due to recent controversy over silicone implant use, however, many researchers are looking for alternative implant substances.

Two of the "backbones" of silicone are silicon and oxygen. Silicon (a nonmettalic chemical element found abundantly in nature) was first isolated in the 1820s. In the 1880s it was combined with other elements to form useful compounds, including silicone. But it was not until the 1940s that E. G. Rochow of the General Electric Company discovered an easy way to form silicone by combining methyl chloride gas with heated silicon and copper. Silicone was used extensively during World War II (1939-1945) to waterproof sensitive electronic parts, like gaskets for search lights and superchargers for aircraft engines. Medical applications include **artificial joints**, eye lenses, the Norplant contraceptive (a device implanted under the skin of a woman's arm that slowly releases an artificial hormone), and breast implants.

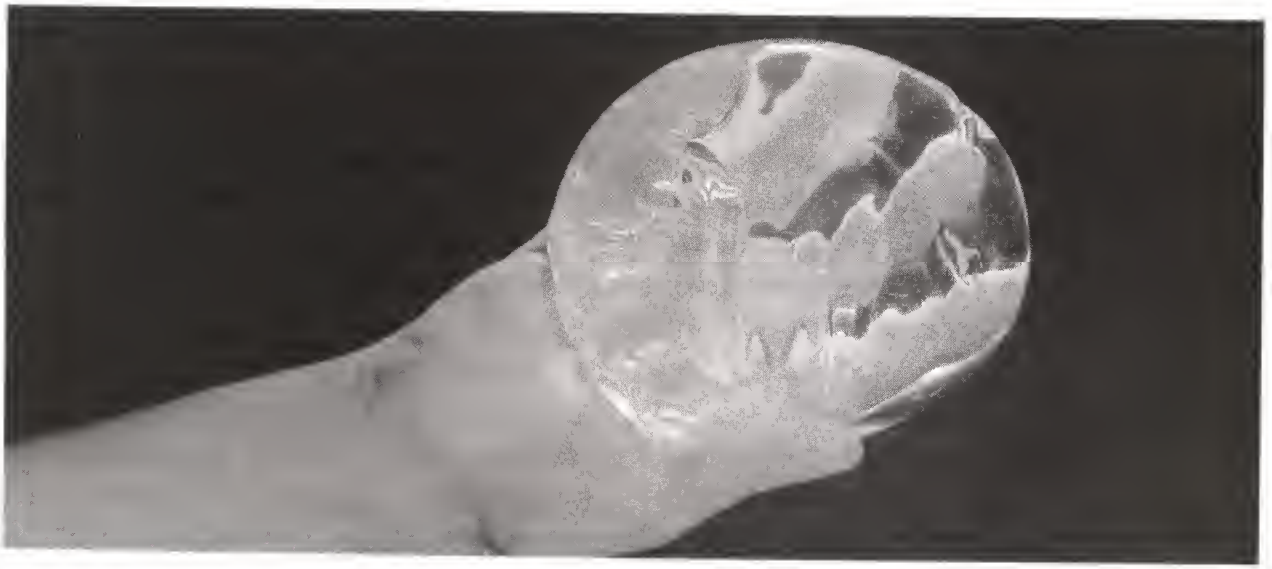
Silicone was first used in breast implants in the early 1960s. These early implants gave women the option of improving their appearance and the ability to reconstruct breasts that had been removed during cancer surgery. In the past thirty-five years, about one million women have had breast implant surgery. Over time, some of these women have experienced problems or complications. These problems have included localized (limited to a specific area) silicone leakage and hardening of the breast due to tightness of scar tissue surrounding the implant.

Since the early 1960s, over one million women have had breast implants.

In the 1980s, some women who experienced silicone leakage or the more rare rupture (breaking) of an implant began to suspect that silicone was responsible for other health problems, particularly connective tissue diseases such as rheumatoid arthritis (a degenerative disease of the joints). In part due to media coverage in the early 1990s, many women became concerned about the safety of their implants, and the Food and Drug Administration (FDA) began to investigate. The FDA found that proper scientific testing of the implants' long-term effects had not been done. As a result, the FDA banned the use of silicone implants in 1992, pending further test results.

Some women—both individually and as part of "class action" (large group) suits—proceeded to launch a series of legal actions against implant manufacturers, particularly Dow Corning (the major manufacturer of silicone breast implants for many years). The legal controversy has continued, while the scientific community has attempted to conduct studies on the actual effects of silicone in the human body. The tests thus far have not shown a decisive link between silicone and any of the diseases currently associated with its use in implants. Today, breast implants are still available, but most are filled with saline (salt) solution.

Silicone breast implants have come under fire in recent years due to allegations that links can be made between silicone leakage and a number of serious health problems.



Calcium

Calcium is a chemical element and member of the alkaline-earth metals group. In its pure form, calcium is a silvery-white substance. Calcium is one of the most abundant substances on Earth, making up about 3.64 percent of the Earth's crust. It is also the fifth most abundant element in the human body. Calcium is necessary for good health. It is essential to muscle contraction and is needed for the transmission of nerve impulses, the clotting (thickening) of blood, and to maintain healthy membranes (thin layers covering cells and organs through which materials, usually liquids and gases, can pass).

Calcium also helps regulate contractions of the most important muscle in the body, the heart. This was discovered in 1882, when British physician Sydney Ringer (1835-1910) showed that a heart would continue to beat in a solution of salt, calcium, and other chemicals. Large amounts of calcium are needed for a developing baby during pregnancy and for the production of mothers' milk. Most of the calcium in the body—about 99 percent—is contained in the bones and teeth. The remaining one percent circulates in the bloodstream where, as American biochemist Elmer McCollum proved in the early 1900s, it is essential for muscle contractions. Bones get their strength and rigidity from calcium, which makes up 70 percent of their weight.

Calcium was not known as an element until the early 1800s, when chemists trying to prove the existence of unknown metals in natural compounds began using the newly discovered phenomenon of electricity to break them apart. English chemist **Sir Humphry Davy,** a pioneer in the

field of electrochemistry, first isolated elemental calcium in 1808 by electrolyzing a mixture of lime and mercuric oxide.

Natural calcium compounds are found most frequently in rocks and minerals. Calcium carbonate is the most abundant of these, making up over 40 percent of the content of limestone. (In fact, calcium's name comes from the Latin word "calx," or limestone). Marble, dolomite, seashells, pearls, and coral also contain large amounts of calcium carbonate. Today, the compound is used in toothpastes and antacid medicines, and is also an ingredient in white paint.

Calcium Carbide

Another important compound of calcium is carbide, which was discovered by German chemist Friedrich Wöhler. In 1892 American scientist T. L. Willson produced calcium carbide by combining lime with carbon and heating the mixture. The result was a hard, brittle crystal that, when exposed to water, yielded calcium hydroxide and acetylene, a flammable gas used in welding. Calcium acetate is used in the production of plastics, and calcium hypochlorite is a bleaching agent and disinfectant.

When it is deficient (lacking) in the diet, calcium is released from the bones to maintain the level needed by the rest of the body. Over time, too little calcium can cause osteoporosis, a progressive weakening of the bones. Another bone disease called rickets can occur if the body does not have enough **vitamin D** to aid in calcium absorption. Rickets has plagued mankind for a long time. Archaeologists have found the bones of humans dating to about 50,000 B.C. that showed evidence of rickets.

Calcium is found in most plants and animals and is necessary for their health. Calcium phosphate is often used a fertilizer to enrich calcium-poor soil. Good sources of calcium in foods are tofu, milk and other dairy products, leafy green vegetables, sesame seeds, seaweeds, beans, almonds, and canned fish that contain the bones, such as sardines and salmon.

Cataract Surgery

A cataract is an opacity, or clouding, of the lens in the eye. The opacity can cause blurred vision and eventual blindness. Light enters the eye through the cornea, which is the transparent covering of the eyeball. Then the light passes through the lens, which bends the light onto the retina at the back of the eye. In an eye with a cataract, light can no longer pass through the clouded part of the lens. Cataracts are often associated with aging and are

thus called "senile cataracts." They can also be caused by diabetes, parathyroid gland abnormalities, Down's syndrome, and other medical conditions. Recent studies suggest that exposure to the **ultraviolet radiation** in sunlight and artificial light during childhood may have an effect on the formation of cataracts in later life.

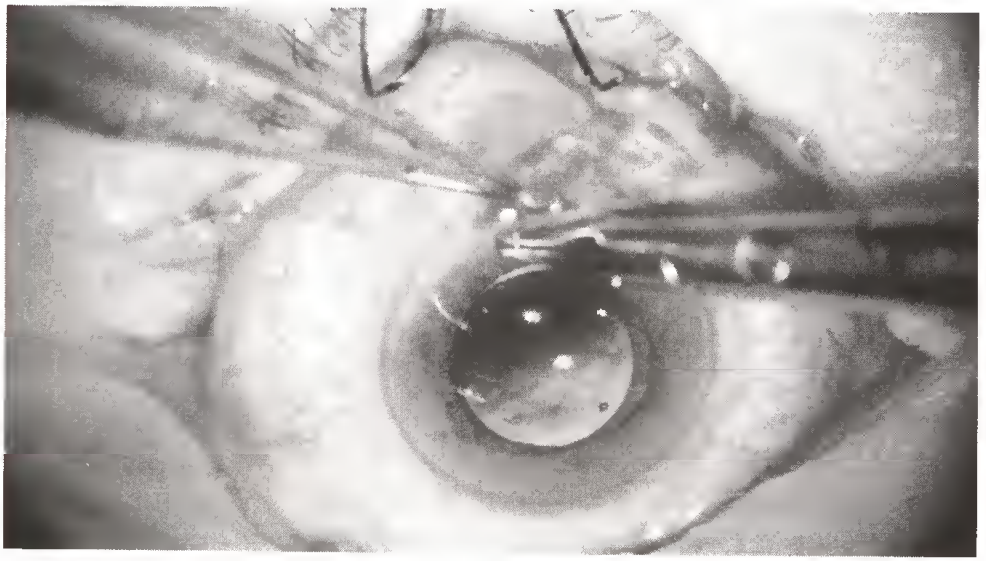
Surgery

Cataract surgery has a long history. It was mentioned in the code of Hammurabi, a Babylonian king who lived 4,000 years ago. The first known cataract operation to extract a clouded lens was performed by J. Daviel, a Frenchman, in 1748. Another well-known surgeon, W. Cheselden, restored sight to a man born blind.

In a surgical procedure called an introcapsular extraction, the entire lens is removed through a cut made along the top edge of the cornea. In this surgery, invented by an American named Kelman in 1976, an **ultrasonic device** actually emulsifies (breaks) the lens into tiny fragments so that it can be aspirated (suctioned) from the eye. A plastic lens is then inserted, and the incision is closed with tiny sutures. Plastic lenses were first invented in 1952 by the English physician Harold Ridley. The plastic lens may completely restore vision, or the patient's vision may require fine-tuning with additional **eyeglasses** or **contact lenses.**

In 1905 Austrian physician Eduard Zirm performed the first known corneal **transplant** (the removal of an object or organ from one body to another) by transplanting the cornea of one person into the eye of a blind person. Basing his work on Zirm, Dr. Elschwig of Prague, Czechoslavakia, also successfully performed a corneal transplant in 1914. Since 1944, eye

Cataracts are often associated with aging, but they also be caused by diabetes and other medical conditions.



Cataract surgery becomes necessary when the lens of the eye becomes "clouded" and no longer allows light to reach the retina.

banks have been established in many places around the world to store donated eyes for transplants.

In 1961, an American physician, Irving S. Cooper, began using a freezing technique known as **cryosurgery** to freeze and destroy damaged tissue. Cooper first used cryosurgery on the damaged brain tissue of Parkinson's disease (a progressive nervous system disorder) patients. Now it is successfully used to remove cataractous lenses. In 1979 Professor Daniele Aron-Rosa performed the first **laser** eye surgery to use the ultra-rapid, pulsated Yag laser. Lasers allows surgeons to work without having to cut the eye. Laser surgery has also been successfully used on corneas and detached (unattached) retinas.

[*See also* **Contact lens; Laser surgery; Ultraviolet radiation**]

Cathode ray tube (CRT)

In the mid to late 1800s, the world experienced a scientific revolution. Phenomena that had never before been truly understood, such as light, heat, and electricity, were systematically explored. Great scientists like Henri Becquerel (1820-1891; French chemist and an authority on luminescent, or light caused by radiant energy, phenomena), **Marie Curie** (1867-1934; Polish-born French physicist who worked extensively with radium) and Thomas Young (1773-1829; English physician and physicist) led the way.

Early Experimentation

Early experiments to solve the riddle of electricity often included the use of anode-cathode tubes (glass tubes that contained an anode at one end and a cathode at the other). When most of the air was evacuated from the tube, an electrical charge could be seen jumping across the gap between the two electrodes. It was English physician and chemist Michael Faraday (1791-1867) who noticed that as the amount of air in the tube decreased, a faint glow between the electrodes could be seen. Faraday was not able to explore this effect completely because technology was not advanced enough to produce a high vacuum within the tube.

Vacuum Tubes

The German team of Heinrich Geissler (1815-1879) and Julius Plucker (1801-1868) pioneered the study of cathode-ray tubes. Geissler was a skilled glassworker, employed by the University of Bonn (Germany) as a maker of scientific instruments. While at the university he met Plucker,

then a young professor. Sometime around 1855, Plucker convinced Geissler to design an apparatus for evacuating (completely emptying) a glass tube. Geissler did just that. He constructed a hand-crank mercury pump that could remove most of the air from a tube. The new vacuum tubes were very popular, and became known as "Geissler's tubes".

Using the improved vacuum tube, Plucker made some startling discoveries. First, he was able to produce a bright stream-like glow between the electrodes. The glow was much brighter than any achieved in previous experiments. Second, he found that the glow responded to a magnetic field. The glow could be moved by a powerful magnet. The discovery indicated that the stream crossing the vacuum was composed of particles rather than rays.

The next scientist to conduct important research using vacuum tubes was Johann Hittorf ((1824-1914) in 1869. A student of Plucker's, Hittorf further improved the method for creating a vacuum within glass tubes of his own design. He observed that the luminescent glow increased dramatically as the pressure within the tube continued to decrease. He also placed tiny obstacles inside the tube in the path between the two electrodes. When a current was applied, the glow would be partially obscured by these obstacles, casting shadows. This further confirmed the idea that the glow was caused by a particle emission.

Crookes' Tube

Probably the most important research using cathode-ray tubes was performed in 1875 by the English physicist William Crookes. In order to confirm the experiments of Plucker and Hittorf, Crookes designed his own vacuum tube from which the air could be almost completely removed. So great an improvement over Geissler's tubes were these that the "Crookes tube" quickly became the standard vacuum tube for use in scientific experiments. Crookes continued Plucker's experiments with magnetic fields, confirming the glow was easily deflected. He also installed tiny vanes within his tubes. As the current was applied the vanes would turn slightly (it was as if they were blown by a gust of wind).

German scientist Eugen Goldstein (1850-1930) first dubbed Crookes's rays "cathode rays" in 1876. In 1892, Phillip Lenard followed up on Heinrich Hertz's discovery that under certain conditions cathode rays could penetrate metal. Lenard succeeded in passing cathode rays through a window of thin metal set into the side of a Crookes tube. The rays exited the tube through the window into the air. Lenard proved that cathode rays were not a phenomenon exclusive to a vacuum. While performing a similar experiment in 1895, the German physicist Wilhelm Roentgen (1845-

1923) accidentally discovered an even more penetrating form of radiation, which he called X-ray radiation.

Practical Uses for Cathode Rays

While many scientists were busy trying to unlock the secrets of cathode rays, others were searching for ways to apply them toward practical ends. The first such application came in 1897 in the form of Karl Ferdinand Braun's oscilloscope. This device used a cathode ray tube to produce luminescence on a chemically treated screen. The cathode rays were allowed to pass through a narrow aperture, effectively focusing them into a beam which appeared on the screen as a dot. The dot was then made to "scan" across the screen according to the frequency of an incoming signal. An observer viewing the oscilloscope's screen would then see a visual representation of an electrical pulse.

During the first three decades of the twentieth century, inventors continued to devise uses for cathode ray technology. Inspired by Braun's oscilloscope, A. A. Campbell-Swinton suggested that a cathode ray tube could be used to project a video image upon a screen. Unfortunately, the technology of the time was unable to match Campbell-Swinton's vision. It was not until 1922 that Philo T. Farnsworth used a magnet to focus a stream of electrons onto a screen, producing a crude image. Though the first of its kind, Farnsworth's invention was quickly superseded by Vladimir Zworykin's kinescope, the ancestor of the modern television.

Today, most forms of image-viewing devices are based upon cathode-ray technology. In addition, electron guns are used widely in scientific and medical applications. One important use for cathode-ray research has been the electron microscope, invented in 1928 by Ernst Ruska. The electron microscope uses a stream of electrons to magnify an image. Because electrons have a very small wavelength, they can be used to magnify objects that are too small to be resolved by visible light. Just as Plucker and Crookes did, Ruska used a strong magnetic field to focus the electron stream into an image.

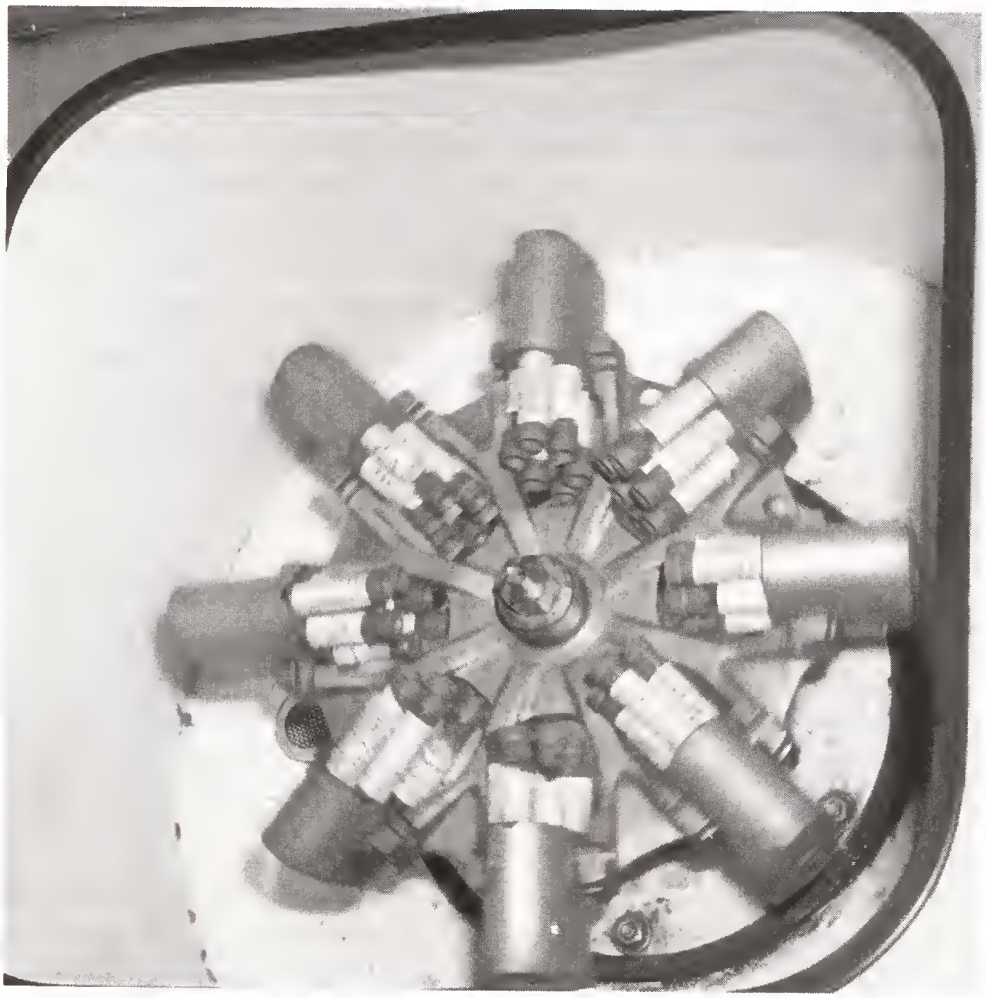
[*See also* **X-ray**]

Centrifuge

Gravity can eventually separate a sediment (material that settles to the bottom of a liquid) from a liquid or separate two liquids which do not mix. The heavier element within a container sinks to the bottom, while the

lighter element rises to the surface. This process is very slow if left up to nature alone. It can also be wasteful, as evidenced by the way farmers used to separate cream from milk. They would let whole milk stand for several hours until the lighter cream rose to the top. They then skimmed off the cream with a wooden spoon, but as much as 40 percent of the cream was left in the milk. Later, small strainer dishes were used to extract the cream, yet this too was a slow process.

In 1877 Swedish inventor Carl Gustaf Patrik de Laval introduced a high-speed centrifugal cream separator. Milk was placed in a chamber where it was heated. Once heated, it was sent through tubes to a container that was spun at 4,000 revolutions per minute by a steam engine. The centrifugal (moving away from the center) force separated the lighter cream, causing it to settle in the center of the container. The heavier milk was pushed to the outer part and forced up a discharge pipe. Thus, only the cream was left in the container. Several years later an improved cream sep-



The modern centrifuge is descended from a high-speed cream separator that was developed by Carl Gustaf Patrik de Laval in 1877.

arator was introduced with the capability for self-skimming and self-emptying. This type of separator can be used for other purposes and can extract impurities from lubricating oils, beer and wine, and other substances.

Spin Dryers

Other types of centrifuges were created in which spin dryers were used for filtering solids. In these dryers, a perforated (full of holes) drum is spun, driving any separated liquids to the outside where they were collected. Spin dryers can now develop accelerations of up to 2,000 times the force of gravity. They are used in the food, chemical, and mineral industries to separate water from all sorts of solids. Other centrifuges remove blood serum (plasma) from the heavier blood cells.

Scientists needed faster rotations for separating smaller particles. Particles, like DNA (deoxyribonucleic acid), proteins, and viruses are too small to settle out with normal gravity. The banging of water molecules is enough to keep the particles from separating. The key to separating smaller particles was to build an ultracentrifuge. A centrifuge that could spin fast enough to cause these small particles to settle out. In 1923 the Swedish chemist Theodor Svedberg developed a device that could spin fast enough to create gravity over 100,000 times normal. It could take small samples in glass containers, balance them on a cushion of air, and send jets of compressed air that touched the outer surface. By 1936 Svedberg had produced an ultracentrifuge that spun at 120,000 times per minute and created a centrifugal force equal to 525,000 times that of normal gravity. Newer models can accelerate samples to 2,000,000 times the force of gravity.

The ultracentrifuge enabled biologists, biochemists, physicians, and other life scientists to examine viruses, cell nuclei, small parts within cells, and individual protein and nucleic acid molecules. These new tools helped make the **genetic engineering** field ripe with possibility.

Cesarean section

Cesarean section is the removal of an unborn child from the uterus by means of surgical incision through the abdominal wall. Originally practiced only on dead women, cesarean section today is a common and relatively safe birth method.

Surgical removal of a fetus (name given to unborn young from the end of the eighth week of development to birth) from a dead or dying mother was mandated for religious purposes by several ancient cultures.

Examples of these mandates (or rules) were chronicled in Egypt in 3000 B.C. and in India in 1500 B.C.. In these cases, a cesarean procedure was performed in order to provide separate burials for the mother and the baby. The ancient Roman law code, known as *lex caesaria* (the "Law of the Caesars"), sometimes ordered this procedure in an attempt to save the baby. It is the law's name that is the probable source of the operation's name, not the legend about the unlikely surgical birth of emperor Julius Caesar (100-144 B.C.).

Sporadic attempts to perform cesarean sections as a means of saving both mother and baby seem to have occurred in medieval Europe. Records from Frankfurt-am-Main, Germany, claim seven cesareans were performed there before 1411. A French physician reported fifteen cesarean operations by 1581. It is unlikely that many of these cases had nonfatal consequences for the mother because of the incredibly crude surgical practices of the times.

Early Successes

One of the earliest reports of a successful cesarean operation dates to the year 1500, when a Swiss pork butcher or sow gelder named Jacob Nufer used his practiced skills to deliver his own wife of their child. The first reliably documented cesarean section was performed by Jeremiah Trautman in 1610 in Wittenberg, Germany. A renowned Dutch physician, Hendrik van Roonhuyze, championed the procedure. van Roonhuyze included illustrations of his method of cesarean incision in his 1663 book on operative gynecology. Cesarean section came to the British Isles in 1738, when an Irish midwife named Mary Donally performed a successful emergency operation. Cesarean delivery was practiced successfully in the United States by John Lambert of Ohio in 1827 and Francois Prevost in Louisiana before 1832. A patient of William Gibson of Baltimore, Maryland, lived for fifty years after her first delivery of two cesarean births in 1835.

Although cesarean delivery could be successful, the operation was largely avoided throughout the eighteenth and most of the nineteenth century because the maternal (mother's) mortality rate associated with the surgery was between 50 and 75 percent. Also, **anesthesia** had not been discovered, making the operation an agonizing procedure for the mother. In addition, massive infection was an extremely likely outcome and internal bleeding problems killed many mothers.

Cesarean delivery was largely avoided throughout the eighteenth and most of the nineteenth century because the maternal mortality rate associated with the surgery was between 50 and 75 percent.

Modern Advances

Once anesthesia, **antisepsis**, and uterine suture (sewing with stitches) became standard, cesarean delivery became a viable and sensible option.

During the early 1900s cesarean section gradually replaced other alternatives such as high forceps (an instrument resembling tongs used to help pull a baby from the birth canal) delivery, cutting of the pubic bone, and destruction of the fetus. As the birthplace moved from home to hospital, the cesarean mortality rate dropped to near zero by 1960. The rate of cesarean delivery however, rose dramatically. This rate was spurred on by a doctor's 1916 dictum (saying) "Once a cesarean, always a cesarean". Today, 25 of every 100 births in the United States are by cesarean section.

Chain, Ernst Boris

Ernst Boris Chain (1906-1979) was one of three men (Australian biochemist **Howard Walter Florey** and Scottish chemist **Alexander Fleming** completed the trio) who discovered and developed the first **antibiotic, penicillin**. Chain's parents were Russian Jews who had emigrated to Berlin, Germany. He was educated at a German university, but emigrated to Britain in 1933 to work at Cambridge University, where he studied **enzymes** and molds. His first discovery was about the behavior of bacteria. Chain found that they helped to spread infections by excreting an enzyme.

Ernst Boris Chain.

Chain began his collaboration with Florey (1898-1968) in 1939. Chain had noticed Fleming's (1881-1955) writings about how molds, essential to the development of penicillin, had killed bacteria in one of his sample dishes. Unfortunately, Fleming had not found a way to purify or concentrate his discovery. By 1941 Chain and Florey had accomplished what Fleming had not be able to do: isolate and test penicillin on humans. The results of the tests were outstanding, and mass production of penicillin soon followed. Chain also discovered that bacteria could develop a resistance to penicillin, so he worked on the development of other antibiotics as well.

After he shared the 1945 Nobel Prize with Florey and Fleming, Chain noticed that many post-war universities had gone back to an atmosphere of competitive, secretive research, which he did not like. In response he started two new research institutions, one in Rome and one in

London, which maintained an atmosphere of cooperation and openness, thus setting the trend for our international research collaborations of today.

[*See also* **Enzyme**]

Chemotherapy

Treating or preventing any disease or medical condition with chemicals or drugs is known as chemotherapy. Many people now connect the word chemotherapy with cancer treatment, but chemotherapy was first developed for other infectious diseases, such as syphilis (a sexually transmitted disease) and diphtheria (pronounced "dif-*theer*-iyah"; an infectious disease in which a membrane—or thin cover—forms, usually in the throat). Chemotherapy drugs are systemic medications, that is they act throughout the entire body. The first chemotherapy drugs, or agents, were the sulfa drugs, or sulfonamides, which began to be used in the 1930s. **Penicillin** and other **antibiotics** came out in the 1940s. **Hormones** began to be used as chemotherapy agents in the 1950s.

The "Magic Bullet"

In the late 1800s two German bacteriologists, **Emil von Behring** (1854-1917) and **Paul Ehrlich** (1854-1915), produced diphtheria antitoxin, which was first given to human patients in 1891. The antitoxin made the recipient immune to catching the infectious throat disease. Then Ehrlich experimented with dyes and discovered that certain dyes stained certain types of cells. Ehrlich succeeded in staining the cell responsible for causing the contagious lung disease tuberculosis. Identifying the cause of infectious diseases was necessary before drugs could be developed to control or cure them. Ehrlich eventually discovered an arsenic compound that cured the sexually transmitted disease syphilis. He also discovered a dye that treated African sleeping sickness.

Ehrlich believed that "magic bullets" could be produced, substances that would only affect the invading cells that caused disease, but not harm the body as well. Ehrlich's work is credited with starting the age of chemotherapy, but the "magic bullet" has been harder to realize because chemotherapy drugs have become stronger and more toxic.

Viral Disease Targeted

Acyclovir is the first chemotherapeutic agent to be effective against viruses. Two American biochemists, George Hitchings (1905-) and

Gertrude B. Elion (1918-), produced acyclovir in the early 1950s to treat herpes infections. For their discovery, Hitchings and Elion shared the 1988 Nobel Prize for medicine with the British pharmacologist Sir James Whyte Black (1924-).

Other viral infections benefiting from chemotherapy are influenza (flu) and Acquired Immune Deficiency Syndrome (AIDS). In the case of AIDS, many drugs have been tested, but the United States Food and Drug Administration (FDA) has only approved of two chemotherapies: azidothymidine (AZT) and dideoxyinosine (DDI). AZT and DDI stop the human immunodeficiency virus (HIV) from reproducing, and DDI is used for AIDS patients who cannot tolerate AZT.

Treating Cancer

The word cancer is actually just a general word for the usually fatal, aggressive diseases that are part of a larger class of diseases, the neoplasms.

A patient undergoes chemotherapy. Chemotherapy drugs are systemic medications, that is they act throughout the entire body.

Neoplasm cells are different from normal cells because they grow more rapidly or are obviously abnormal. They can be either benign (harmless) or malignant (cancerous). In the mid-1940s two cancers benefited from chemotherapy treatment: prostate cancer, which affects a gland near the bladder of males, and breast cancer. In these cases, the chemotherapy agents were **sex hormones**, estrogens for prostate cancer, and estrogens and androgens for breast cancer. There are now 50 chemotherapy agents in use against cancer, but researchers find that the search for new drugs is difficult and lengthy.

Systemic Action

Chemotherapy has proven to be a good treatment choice for many cancers because the drugs act systemically. The drugs may also be combined with other drugs and with radiation and/or surgery. Recovery from the very aggressive cancers may not always be possible, but chemotherapy often extends the patient's useful life and may slow down the cancer's rate of growth. Anti-cancer drugs tend to be highly toxic—-to cancer cells as well as healthy cells—-and they produce severe side effects, such as nausea, tiredness, and hair loss. Combining drugs seems to sidestep the problem of resistance to therapy, which is more likely to occur when one drug alone is used. Chemotherapy drugs have also proven to be as effective as bone marrow transplants for children with acute myeloid leukemia, which sidesteps the difficult problem of finding a suitable bone marrow donor.

Sources for chemotherapy agents have been found in plants, such as colchicine from the autumn crocus, vincristine and vinblastine from the pink periwinkle, and taxol from the bark of yew trees. The alkaloids found in these plants seem to stop cancer cells from reproducing. Taxol was discovered in 1978 and began clinical trials in 1993. Anthracyclines are another class of naturally occurring substances that are useful against breast, lung, thyroid, stomach, and other cancers. **Antibiotics** are another treatment option. Female reproductive cancer and brain tumors are among the cancers that show sensitivity to antibiotics.

[*See also* **Hormone; Penicillin**]

Chloroform

Chloroform is another name for the colorless, dense, liquid chemical compound trichloromethane. It is nonflammable and has a pleasant odor and a burning, sweet taste. Chloroform is about 40 times as sweet as sugar.

Nearly insoluble (unable to be dissolved) in water, chloroform easily dissolves in alcohol, **ether,** acetone, gasoline, and other organic solvents. It can be prepared by the chlorination of ethyl alcohol or of methane. Once made from acetone and bleaching powder, chloroform is now prepared by the photochemical reaction of methane with chlorine.

Chloroform used for industrial purposes is usually made by the action of iron and acid on carbon tetrachloride. It is important as a solvent for gums, fats, resins, elements like sulfur and **iodine,** and many other organic compounds. Chloroform is also used to extract and purify **penicillin.**

Anesthetic Chloroform

Chloroform was popular as an **anesthetic** from the mid-1800s to around 1900, but it was found to cause death from paralysis of the heart in one patient in about 3,000. It also depresses most of the body's other organs, including the blood vessels, liver, pancreas, and kidneys. It is toxic to the liver. Oxygen-gas mixtures (oxygen with **nitrous oxide,** for example) regained use in anesthesia after 1900, and chloroform was replaced by safer compounds after about 1940. Years ago, chloroform was widely used in cough syrups, liniments, sedatives, and pain relievers. More recently, it has been listed as a carcinogen by the U.S. Environmental Protection Agency and been banned for use in drug, cosmetic, and food products since 1976.

The compound was discovered in 1831 by scientists in three different countries working at the same time: Samuel Guthrie (1782-1848) of the United States, Eugene Soubeiran (1797-1858) of France, and Justus von Liebig of Germany. (Guthrie, an American chemist and physician, also introduced **Edward Jenner**'s vaccination technique to the United States.) M. J. Dumas of Paris described the composition of the new liquid and gave it the name "chloroform" in 1834 or 1835. The Frenchman Marie-Jean-Pierre Flourens (1794-1867) noted the anesthetic, but toxic, effect of chloroform on animals in March 1847.

Simpson Discovers Chloroform's Potency

Sir James Young Simpson, an eminent Scottish obstetrician, introduced the medical use of chloroform as an anesthetic in Edinburgh, Scotland, in November 1847. Earlier that year, Simpson had begun using ether to relieve the pain of childbirth, but was dissatisfied with some of ether's drawbacks, such as its disagreeable smell, the large quantities required, and the lung irritation it caused. Ether was also explosive, which was a problem for doctors who often worked by candlelight in rooms heated by fireplaces. A Liverpool chemist, David Waldie, suggested that Simpson try chloroform. On the evening of November 4, 1847, Simpson and two doctor friends inhaled some

chloroform and, after feeling very happy and talkative, promptly passed out. Impressed with chloroform's potency and rapid effects, Simpson immediately began using it in his obstetrical practice. The first baby born to a mother who received chloroform for pain was named Anaesthesia.

Scottish clergymen quickly objected to this use of anesthesia, insisting the pain of childbirth was ordained by God. Simpson countered by citing the biblical account of the deep sleep cast on Adam when God took the first man's rib and used it to make Eve. The argument continued until 1853, when Queen Victoria (ruler of England from 1837-1901) chose to be chloroformed for the birth of her son Prince Leopold (1853-1884). This event quieted the clergy and made chloroform the most fashionable anesthetic—especially in England— for the next 50 years.

Although chloroform did carry some risk of heart failure, it was more pleasant to take and more powerful than ether. Queen Victoria's anesthetist, Dr. John Snow (1813-1858), developed an inhaler to regulate the amount of chloroform administered to a patient so that he or she felt no pain but remained conscious.

[*See also* **Anesthesia**]

Chromatography

Chromatography works by separating the individual parts of a mixture so that each one can be analyzed and identified. In the decades since its invention, the chromatograph has become an essential piece of equipment in biochemical laboratories. Using the analytical technique of chromatography, scientists can tell what chemical compounds are present in complex mixtures. These mixtures include such diverse things as smog, cigarette smoke, petroleum products, or even coffee aroma. Without chromatography, chemists might not have been able to synthesize proteins such as **insulin** or understand how plants use the sun's energy to make food.

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The First Chromatograph

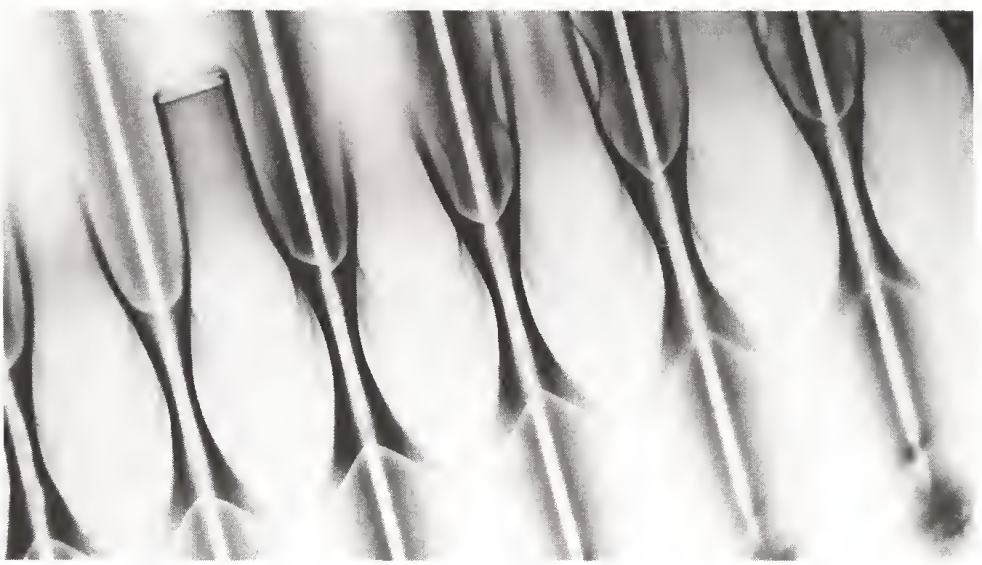
The first chromatograph was invented by Russian botanist Mikhail Semenovich Tsvett (1872-1919). While working in Poland, Tsvett was looking for a method of separating a mixture of plant pigments (tints) which are chemically very similar to each other. To isolate different types of chlorophyll, he trickled a mixture of dissolved pigments through a glass tube packed with calcium carbonate powder. As the solution washed downward, each pigment stuck to the powder with a different degree of strength,

creating a series of colored bands. Each band of color represented a different substance. Tsvett referred to the colored bands as a chromatogram. He also suggested that the technique (now called adsorption chromatography) could be used to separate colorless substances.

Although Tsvett published a report of his work in the early 1900s, chemists paid very little attention to it. There were a few reasons for ignoring the work. First, the report was written in Russian, which few Western chemists of the time read. Second, the technique may have seemed too simple to chemists who were used to relying on lengthy extraction, crystallization, or distillation processes to separate mixtures. Within a few years, Tsvett's technique was rediscovered. The rediscovery was by the German organic chemist Richard Martin Willstatter (1872-1942), who was also studying chlorophyll. By introducing chromatography to Western European scientists, Willstatter helped establish one of the most versatile analytical techniques known to chemistry.

Ion-Exchange Chromatography

Chromatography was found to work on almost all kinds of mixtures, including colorless ones, just as Tsvett had predicted. Absorbing powders were discovered that perform better than **calcium** carbonate for separating ordinary molecules. Also, compounds known as "zeolites" were introduced to separate individual ions, or electrically charged particles, in a process called ion-exchange chromatography. American chemist Frank Harold Spedding adapted this technique to the separation of rare-earth metals. In the 1930s, synthetic resins were developed for complex ion-exchange



A chromatography extract.

processes. During World War II (1939-1945), life rafts were equipped with survival kits that contained resins for removing most salts from seawater.

Paper chromatography

The most dramatic advance in the history of chromatography took place in 1944. It was then that scientists discovered that a strip of porous (full of small holes) filter paper could substitute for the column of absorbing powder. The technique was called paper chromatography. A drop of the mixture to be separated is placed on the paper, then one edge is dipped into a solvent (a substance that dissolves). The solvent spreads across the paper, carrying the mixture's components with it.

When the components are finished spreading, the paper is dried and sprayed with a reagent that reveals a change in color. Because the components move at different speeds, they show up as distinct, physically separated spots that can be cut out with scissors and further analyzed. The paper method is a type of partition chromatography, which is based on differences in solubility (the measured rate at which one substance will dissolve in another) rather than differences in adsorption. One of its advantages is that it requires only a small sample of material.

Martin and Synge

Paper chromatography was invented by two British biochemists, Archer John Porter Martin (1910-) and Richard Laurence Millington Synge (1914-). In 1941 Martin and Synge began working together on proteins, which are made up of chains of amino acids. The duo was trying to characterize a particular protein by determining the precise numbers of each amino acid present. Amino acids are so similar to each other, however, that the problem of separating them had defeated a whole generation of biochemists. Martin and Synge's development of paper chromatography to solve this problem was an instant success. It worked not only on amino acids but also on various other mixtures. The two scientists were awarded the 1952 Nobel Prize in chemistry for their work.

Martin and Synge's research led to a number of other important scientific advances. After Synge determined the structure of an **antibiotic** peptide called "Gramicidin-S," Frederick Sanger (1918-) used paper chromatography to figure out the structure of the insulin molecule. He determined the number of amino acids in it as well as the order in which they occurred. Insulin is now used to control blood sugar levels in people afflicted with diabetes.

The same technique was used by Melvin Calvin (1911-) during the 1950s. Calvin discovered the complex series of reactions that enable green

plants to convert solar energy into the chemical energy stored in food. Working with green algal (algae) cells, Calvin interrupted the photosynthetic process (process by which plants that contain chlorophyll use light to change carbon dioxide and water to carbohydrates) at different stages by plunging the cells into alcohol. Then he crushed them and separated their components via paper chromatography. Calvin was thus able to identify at least ten different intermediate products that had been created within a few seconds.

Paper chromatography was also used by Austrian-American biochemist Erwin Chargaff (1905-), who modified the technique to study the components of the nucleic acid molecule. His research revealed four components, or nitrogenous bases, that occur in pairs. British biochemists **James Dewey Watson** and **Francis Harry Compton Crick later** used these results to work out the structure of DNA (deoxyribonucleic acid).

Gas chromatography

In addition to inventing paper chromatography, Martin developed another technique called gas chromatography. The process allows chemists to separate mixtures of gases, or substances that can be vaporized or gasified by heat. Instead of a liquid solvent, helium gas is usually used to force the mixture through a column and separate the gaseous components. Martin and his colleague A. T. James first used gas chromatography to microanalyze fatty acids.

The widespread acceptance of gas chromatography is unique in the laboratory instrumentation field. Today it is used in almost every branch of the chemical industry, particularly in the production of petrochemicals from oil and natural gas. One of the most common fixtures in biochemical laboratories is "GCMS" (gas chromatography, mass spectrometry) analytical equipment. This equipment uses gas chromatography to separate individual components from complex organic mixtures, then uses mass spectrometry to identify each component.

Thin-Layer Chromatography

Recently, chromatography has evolved into even more sophisticated analytical techniques. In thin-layer chromatography, for example, an alumina gel, silica gel, or other finely divided solid is spread onto a glass plate in a thin, uniform layer. This takes the place of filter paper in the chromatographic process. The technique is not only faster than paper chromatography, but it can also separate smaller quantities of pure components. It is often used in the pharmaceutical industry to isolate **penicillin** and other antibiotics.

Cloning

A clone is a group of genetically identical cells descended from a single common ancestor. Cloning is one method for producing identical twins. After an egg is fertilized, it begins to divide repeatedly. If the egg completely separates during the two-cell stage, identical twins will result. Both individuals will have exactly the same combination of **genes** (genotype) and each will have the same physical characteristics (phenotype). This is an example of how exact duplicates can naturally occur through sexual reproduction.

Science has capitalized on the mechanisms of cellular reproduction to produce clones. Advances in biotechnology since the 1970s have enabled livestock breeders to clone virtually unlimited numbers of identical animals from a single embryo. This allows the precise duplication of an animal with desired characteristics.

In 1979 veterinarian Steen Willadsen developed a way to divide sheep embryos in half at the two-cell stage, making clones possible. In the next few years, several scientists made further strides in this area with both sheep and cattle embryos. A team developed a simplified method of dividing and cloning sheep embryos in 1984.

Cloning is one area of genetics that is advancing very rapidly, and it is therefore very controversial. If this technology is ever applied to humans, who will decide which genes are "desired" and should be cloned? This is only one of many important questions that have arisen as a result of genetic cloning.

Science has capitalized on the mechanisms of cellular reproduction to produce clones.

A sample of "gene footprints" used in a DNA research study. As cloning experimentation becomes more sophisticated, the role DNA plays in the transplantation of genetic material is coming under close scrutiny.

Dairy Farmers Use Cloning Techniques

As an example of cloning techniques, dairy farmers trying to clone a cow with high milk-producing qualities begin by artificially inseminating a high-producing cow with the sperm from a prize bull. The resulting embryo, which contains the entire genetic instructions needed to form a complete calf, develops within its mother. After some time, the embryo divides into a mass of 32 identical cells. The embryo is then carefully removed from the mother cow and separated into 32 separate cells. Finally, after microsurgery on the cells, each new embryo is transplanted into 32 different carrier cows, where it develops fully.

After a normal pregnancy, each carrier cow gives birth to a calf that is genetically identical to the 31 other calves derived from the original 32 cell embryo. Each calf is a clone. The trait for increased milk production has been cloned so that the farmer now has 32 high milk-producing cows instead of just one. Cloning technology has enabled breeders to develop lines of cattle, sheep, and cotton plants that respectively produce more milk, wool, and cotton.

Cocaine

Cocaine is a powerful drug of the stimulant-euphoriant class that is obtained from an alkaloid in the leaves of the coca plant, a shrub or tree that grows in the South American countries of Peru and Bolivia. The processed drug is a white, crystalline compound called benzoylmethylecgonine. It is a central nervous system stimulant, which means it temporarily produces euphoria (a feeling of well-being), prevents drowsiness and fatigue, increases physical energy, heart rate and body temperature, decreases appetite, and increases talkativeness. Cocaine can also cause the user to become irritable, and have hallucinations (strange visions). An overdose of cocaine can cause trembling, vomiting, convulsions, and a depression of the central nervous system. This depression can cause breathing to stop or heart failure. Because it is so highly addictive, cocaine is classified as a narcotic and is controlled by federal drug abuse laws in the United States.

The Indians of South America have chewed the leaves of the coca plant for many generations to help them overcome fatigue and hunger, stay alert, and have greater stamina in the high elevations of the Andes Moun-

tains; the leaves also numb the mouth and stomach. Coca leaves were chewed by Inca runners who carried messages long distances over the mountains and probably by workers who built the Inca road system. Many pottery figurines of early South America show men and women chewing coca leaves, often with expressions of great pleasure on their faces.

Early Research

Albert Niemann (1880-1921) separated the alkaloid cocaine from the dried leaves of the coca plant in 1860. He studied the white powder and named it cocaine, also noting the temporary numbing effect the compound had on his tongue. During the 1880s in Vienna, Austria, Sigmund Freud (1856-1939) studied cocaine as a treatment for **morphine** addiction. Freud suggested the possible use of cocaine as a local **anesthetic** to Viennese colleagues Leopold Königstein, a professor of ophthalmology (the medical study of the eye and diseases of the eye), and Carl Koller (1857-1944), a young ophthalmologist (doctor specializing in eye diseases).

Because it is so highly addictive, cocaine is classified as a narcotic and is controlled by federal drug abuse laws in the United States.

Koller experimented on animals and then presented his findings to the Congress of Ophthalmology in Heidelberg, Germany, in 1884. He demonstrated the successful use of cocaine as a local anesthetic during eye surgery. Koller's findings were accepted enthusiastically. Koller himself emigrated to the United States in 1888 and established practice in New York City, where he died in 1944. Cocaine was used widely for ophthalmological procedures until it was discovered that it causes damage to the cornea (the transparent part of the eye that covers the iris and the pupil). This combined with its potential for drug abuse has resulted in cocaine's being used today only as a topical (given for one part of the body) anesthetic, mainly in the upper respiratory passages (nose and throat).

Local Anesthesia

American doctor William Halsted soon followed up on Koller's work by experimenting with cocaine injection into nerves to produce local anesthesia. By the end of 1885, Halsted had performed over 1,000 operations using cocaine as an anesthetic. Unfortunately, Halsted also discovered another of cocaine's properties. He became addicted to the substance and spent many years overcoming his dependence. Harvey Cushing (1869-1939), a student of Halsted's, coined the term "regional anesthesia" for this use of cocaine, in contrast to the "general anesthesia" produced by **ether,** a gas formerly used for anesthesia in surgery. Later in 1855, Leonard Corning (1855-1939), a New York neurologist, injected a cocaine solution as a spinal anesthesia. German doctor Carl L. Schleich (1859-1922) of Berlin used a cocaine solution for infiltration anesthesia in 1892.

Cocaine and Addiction

For many years, the addictive properties of cocaine went unrecognized. As a pain reliever and stimulant, the drug was a common ingredient in the very popular **patent medicines** of the late 1800s and early 1900s. Doctors freely prescribed cocaine for any number of ailments. Once the addictive dangers became known, scientists concentrated on developing synthetic substitutes for the anesthetic properties of cocaine. One of the first of these was **Novocain.** Today cocaine is only occasionally used medically, as a local anesthetic applied to the surface of the skin for some kinds of surgery. It is not prepared for internal use or for injection as medicine.

Today most cocaine is purchased and used illegally. Cocaine hydrochloride, a dry white powder also called "coke" or "snow" is often inhaled ("snorted") through a thin tube or straw inserted into the nostril. It is absorbed into the bloodstream through the nasal (nose) mucous membranes. Cocaine is sometimes injected into a vein and sometimes smoked in a purified form through a water pipe, called "freebasing." The most potent form of cocaine, "crack," is shaped into pellets and smoked using special equipment. The widespread use of cocaine and the resulting increase in violence associated with drug dealing was an important factor in stimulating the "war on drugs" in the United States that has continued since the 1980s, when cocaine abuse was at its peak.

Long-term use of cocaine can lead to skin sores, damage to the septum of the nose, weight loss, and damage to the nervous system. Bad mental effects include restlessness, anxiety, irritability, and sometimes paranoid psychosis. When a person stops using cocaine, he or she will experience craving for the drug, long periods of sleep, depression, fatigue, and exhaustion. Because withdrawal from cocaine does not produce extreme and dangerous physical symptoms like those caused by withdrawal from **barbiturates,** doctors consider cocaine to be more psychologically addictive than physically addictive.

[*See also* **Anesthesia**]

Codeine

Like **morphine,** codeine is an alkaloid (a naturally occurring base) of **opium,** a drug made from the milky juice of unripe seed capsules of the opium poppy plant. The opium poppy was once native to Asia Minor (a large penninsula in western Asia between the Black Sea and the Mediter-

ranean), but it is now grown legally and illegally in many parts of the world. Codeine, morphine, opium, heroin, and other opium alkaloids—the opioids—make up the class of drugs known as the narcotic analgesics. Because of their ability to relieve pain, narcotic analgesics have been some of the most important drugs in medicine.

An Ancient Pain Reliever

Opium is believed to have been used by the people of Babylonia (an ancient empire in southwest Asia) in 4000 B.C. as a pain reliever and to promote sleep. The first undisputed (certain) writings about poppy juice were by Greek philosopher Theophrastus in the third century B.C. Highly praised by peoples of many civilizations since that time, opium preparations were given the name laudanum (from the Latin word "laudare," meaning "to praise") by the Swiss physician Paracelsus (1493-1541). Beginning in the late 1600s until the discovery of **anesthesia** in the mid-1800s, a preparation of alcohol and opium, usually given in whisky or rum, was the drug most widely used to prepare patients for surgery.

Although opioids may be physiologically addicting in high doses, they are widely used. The use of heroin, however, is prohibited in the United States today, even in medicine. The abuse of opioids became worse with the introduction of the hypodermic **syringe** (needle), which made it easier to use opioids more frequently and in greater amounts. In early times, opium was usually smoked or eaten.

Today only a few opioids—mainly codeine, morphine, and papaverine—are useful in medicine. Codeine is the least habit-forming of the opioids. It is used to reduce pain and suppress (lessen) coughing. The amount of codeine that is naturally present in opium is small in relation to the amount of morphine found in opium, but codeine can be synthesized by a chemical change in morphine called methylation. Morphine is the most powerful painkiller available, and papaverine is used as a smooth muscle relaxant.

In the nineteenth century scientists began to separate the active ingredients of opium. This resulted in the isolation (separation) of morphine, codeine, heroin, and other opium alkaloids. When German pharmacist Friedrich Wilhelm Seturner isolated morphine from opium in 1805, a new era in drug production and use began. Soon many other new drugs were obtained by isolating active elements from crude drugs. One of these was codeine, which was discovered and named by Pierre-Jean Robiquet (1780-1840) in 1832. The chemical works of E. Merck, established in 1827 to manufacture morphine, began producing codeine the same year the drug was discovered. Years later, Thomas Anderson (1819-1874), a professor of

chemistry at the University of Glasgow, Scotland, described the elemental makeup of codeine.

Cocaine Use Today

Today, codeine is commonly used in prescription drugs in combination with **aspirin** or acetaminophen to relieve pain, which it does by altering the way the brain reacts to painful sensations. It is also a common ingredient in prescription cough medicines. Codeine depresses the cough reflex by acting on a cough center in the part of the brain known as the medulla. It can be addictive, which is why it is only available by prescription. Many cough suppressants that do not contain codeine are available without a prescription. Codeine and other opioids cause nausea and vomiting in some patients.

Opium, morphine, and codeine are among drugs classified as Schedule II in the U.S. Comprehensive Drug Abuse Prevention and Control Act of 1970. This means they have a high potential for abuse and a severe likelihood of causing physical or psychological dependence. Because of this, the federal government regulates how they are produced and how they are dispensed by pharmacists. It is illegal to make, sell, or use these drugs in any way that does not follow these governmental rules.

In the 1970s scientists discovered naturally occurring opioids in the brai called **enkephalins.** Many scientists believe a person becomes addicted to opioids because of a deficiency in these natural substances.

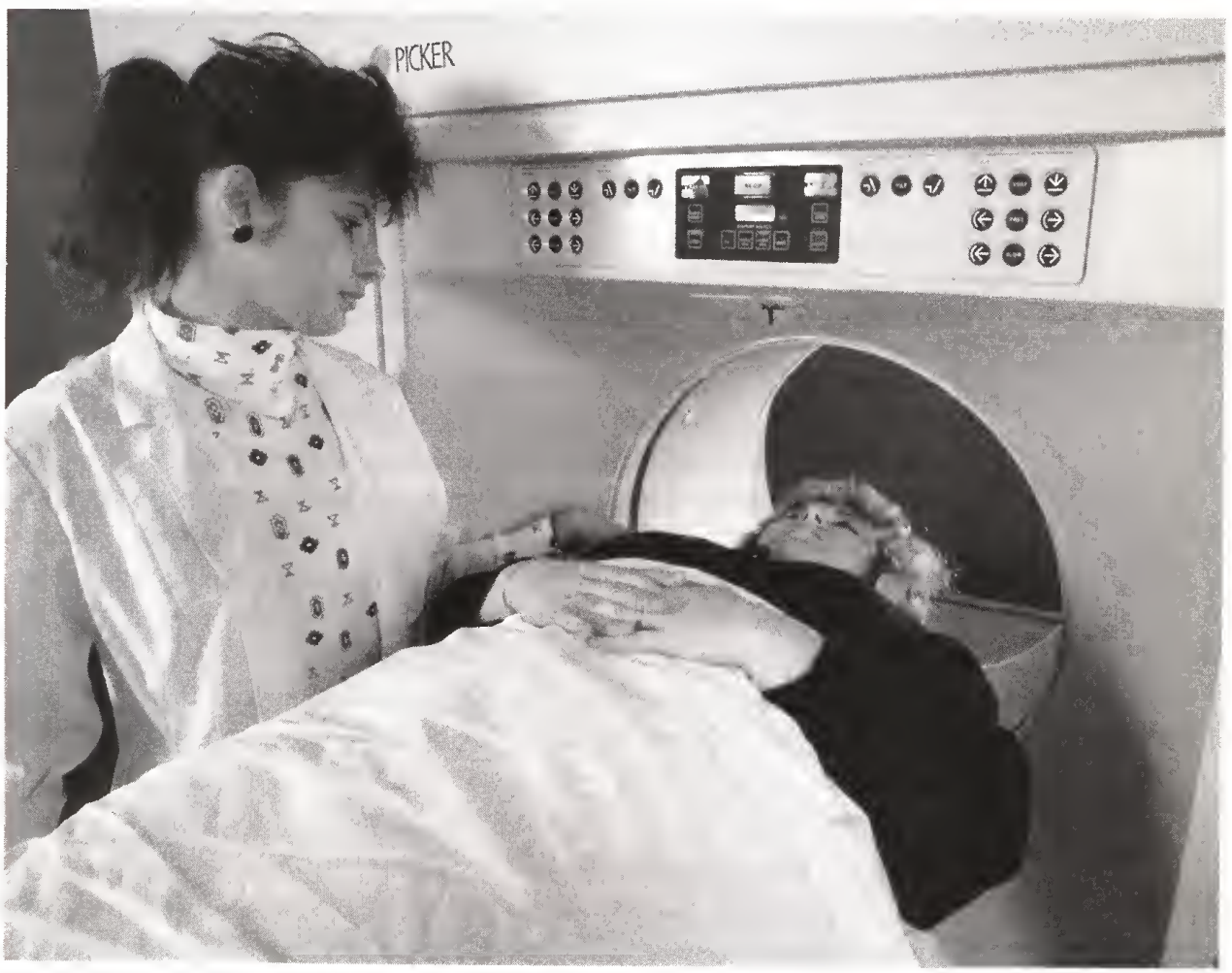
Computerized Axial Tomography

A computerized axial tomography (CAT) scan is a special type of **X-ray** used for viewing the internal organs of patients. Although a regular chest X-ray can show the heart and lungs, the CAT scan can show the same organs but with detail 100 times greater and with little or no additional irradiation (exposure to radiation).

In the late 1960s Alan Cormack, an American physicist, and Godfrey Hounsfield, an English electrical engineer, independently developed a way to produce a three-dimensional image of the parts of the body, (called tomogram) by taking many different X-ray cross sections and combining them. Eventually, the two would share a 1979 Nobel Prize for medicine for their work, research which led to development of the CAT scanner.

Cormack was the first to construct a machine to "shoot" tomograms. His first model used a thin beam of X-rays aimed at one part of the body but taken from many different angles. Unfortunately he lacked a system that could process all of the information that one CAT scan produces. The solution to this problem was the computer. Hounsfield began working on his own CAT scanner in 1967. He used a system similar to Cormack's, but he also used a computer. The computer was able to sort all of the X-ray data into a picture. The first CAT scanner took nine days to complete a picture of a preserved human brain. Before it could be used for patients, Hounsfield had to improve its design. Later models required nine hours and eventually only nine minutes. His final apparatus took about five minutes to complete its scan. The first CAT machine of practical use was installed at Atkinson Morley's Hospital in Nimbledon, England, in 1971.

Today the CAT scanner finishes a scan in a few minutes. The pictures can be seen almost immediately on a television monitor, and within 30 minutes the entire scan can be copied to a computer disk. The scan can be



Some CAT scanners use up to 300 X-ray scanners taking 300 pictures each. This results in almost 90,000 X-ray slices or tomograms that the computer must convert into a picture.

stored on the computer or made into a picture that looks like a usual X-ray. The CAT scan data can be transmitted by modem (computer-phone hookup) to another hospital if, for example, a doctor needed to see the results of the CAT scan quickly.

Scanning Procedures

The CAT scanner consists of a flat table on which a patient lies. A tube-shaped device is on either side of the table and is fitted with many X-ray scanners. Before the scan begins, the part of the patient that is to be scanned is moved inside this tube. The CAT scanner rotates 180 degrees around the patient's body and sends out a very thin beam of X-rays. Each X-ray scanner has a detector placed exactly opposite to it. The scanner and detector are built to move together so that when the scanner moves, it is aimed directly at the detector.

During the CAT scan, the scanner sends out a short impulse that is picked up by the detector. After the detector picks up the first signal, the scanner and detector rotate slightly and the same picture is taken again but at a slightly different angle. As the beam travels from the scanner through the patient, it is changed as it goes through bones and organs. The beam that the detector picks up is different from that the scanner emitted. This difference is noted by the computer. It analyzes this data and converts it into electrical impulses that make a picture on a television screen. The amount of data is huge, since some CAT scanners use up to 300 X-ray scanners taking 300 pictures each. This results in almost 90,000 X-ray slices or tomograms that the computer must convert into a picture.

In the 1970s a more advanced tomography technique was developed by Michael Phelps and Edward Hoffman, biophysicists at the UCLA School of Medicine. The duo developed a PET scan (PET is an acronym for positron emission tomography). For this scan, the patient has a radioactive material injected into the bloodstream. This radioactive material is not harmful and it emits positrons, a kind of beta particle (high-speed electron), and gamma rays. The PET scanner reads gamma rays like the CAT scanner reads X-rays. Since certain radioactive material travels to certain parts of the body (for example, **iodine** goes to the thyroid), more detailed pictures of a specific organ can be made.

Scanner Enhancements

CAT scanners have revolutionized the way doctors diagnose and treat patients. Since doctors can now see inside the patients body, the patient is

often spared surgery. If the patient has a cancer in a certain part of the body and surgery is needed, the surgeon will have a clear idea of how big the cancer is, the surrounding tissues it may be affecting, and how much to cut out. If a cancer cannot be cut out, but it can be treated with X-rays, the CAT scanner can precisely map out the exact borders of the cancer and direct the X-rays to only the cancer.

CAT scanners are being continually refined to take pictures faster and faster. This is important for taking pictures of moving things like blood in a vein or artery. Scanners can now detect blockages, called clots or thromboses, in the arteries or veins. Most recently, an ultrafast type of CAT scanning has been developed called EBCT, an acronym for electron beam computed tomography. With this technique a scan can now be taken of the arteries of the heart, called coronary arteries. The scan reveals a cross section of the coronary arteries and shows the amount of **calcium** in the walls of the arteries. If there is too much calcium in the artery walls, it can cause a blockage that will lead to a heart attack. If these blockages are detected early, a heart attack can be prevented by doing a simple operation.

[*See also* **X-ray machine**]

Contact Lens

A contact lens is a small, shell-shaped piece of eyeware used to correct vision. It is placed directly over the cornea (the transparent, or clear, tissue over the pupil and the iris, or colored part of the eye). There are two types of contact lenses. One is the corneal contact lens which covers only the cornea, and the other is the scleral contact lens, which covers the cornea and a part of the sclera (the white part of the eye).

The contact lens is held in place by fluid attraction forces. These forces are easy to demonstrate. If two pieces of glass are placed together with water between them, it is easy to slide the pieces back and forth. But separating the two pieces of glass is very difficult. Today contact lenses are made from plastics and gels, but the original contact lenses were made of glass blown by glassblowers.

Leonardo da Vinci sketched and described several types of optical devices demonstrating the principles of a contact lens.

Contact Lenses in History

It is hard to say when the idea of a contact lens was born. Leonardo da Vinci (1452-1519; Italian painter, scientist and inventor) knew that glass and water affected vision. He sketched and described several types of opti-

cal devices demonstrating the principles of a contact lens. The first description of what was needed to make a contact lens was given by Sir John W. Herschel (1792-1871) in 1823. Three Europeans are generally credited with the invention of the contact lens: Adolf Eugene Fick, Eugene Kalt, and August Müller. In 1888 Fick described the first contact lens with refractive power (the ability to change vision by bending rays of light). Fick's "contact spectacle" was a thin, very small glass bowl. This bowl was placed on the eye, and the area between the bowl and the eyeball was filled with a liquid similar to tears.

On March 20, 1888, a scientific paper was presented in Paris. Delivered by Kalt, the paper described a lens he made to treat keratoconus (a condition of the eye in which the cornea is cone-shaped; normally the cornea has a convex, or bulging outward, shape). Kalt's lens worked by pressing down on the cornea and making it flatter. This improved vision. When plastic contact lens were introduced, they were similar to Kalt's contact lenses. In 1889 Müller, a medical student at the University of Kiel in Germany, started his work on contact lenses. He was very myopic (nearsighted). His lenses were made to more closely match the curvature of the cornea. He knew they would be held in place by the tears between the lens and the cornea.

Between 1920 and 1940, the Zeiss Optical Works of Jena, Germany, and the Mueller Company of Wiesbaden, Germany, were making glass contact lenses. There were problems with eye irritation, however, and it was not possible to wear these lenses very long. Joseph Dallos understood that tears needed to pass between the lens and the cornea. Eventually it would be discovered that, because the cornea does not have its own blood supply, tears bring nutrients to it. Also, because it has no blood supply, the cornea must get its oxygen from the air.

The first disposable lens was introduced by the Johnson & Johnson Company in 1987. Sold under the brand name Acuvue, the lenses were designed to be worn for up to one week, then thrown away.

Plastic Lenses

In 1936 William Feinbloom made the first contact lenses with plastic. These lenses were a hybrid (combination), however, of both plastic and glass. Feinbloom was also the first researcher to file a patent for bifocal (adjusted to two different focal lengths) and trifocal (adjusted to three different focal lengths) contact lenses. In 1936 the Rhom and Haas Company introduced

a new, transparent plastic material called polymethylmethacrylate (PMMA). This material would be the main plastic used in contacts for the next forty years. In 1938, John Mullen and Theodore Obrig developed a technique for making scleral contact lenses with PMMA.

In 1948 Kevin Tuohy was the first person to make a corneal contact lens when his lab partner accidentally cut away the scleral part of a contact lens in production. Tuohy discovered that he could wear just the corneal part of the lens. There were still some problems, however, with making the contact lens fit properly. In 1950 George Butterfield changed the way contacts were made by creating a lens with different curves on the side of the lens next to the eye. This made the contact very similar to the cornea.

The Hydrogel Lens

The hydrogel lens is made of very pliable chemicals. It does not cause very much irritation to the eye. The idea for the hydrogel lens started with Professor Otto Wichterle, a polymer chemist from Czechloslovakia. Wichterle and one of his assistants created a material called hydroxyethylmethacrylate (HEMA). The researchers found that this material caused little irritation to the delicate tissues of the eye. In 1957 Wichterle tried to make contact lenses in a mold using HEMA. Unfortunately the lenses were too thick, and they often tore when anyone tried to get them out of the mold. Eventually, Wichterle was told that he could not get any more money for his research, so he continued his work at home. Over time, he was able to produce contact lenses that were thin and easy to make. In 1972 the Bausch and Lomb company introduced a hydrogel lens that has almost replaced the hard contact lens completely.

In addition to their cosmetic applications, contact lenses offer several medical advantages over **eyeglasses.** When cataracts (a disease of the lens causing it to get cloudy) are removed, contact lens are more effective than glasses in restoring sight. Unlike glasses, contact lenses can improve the vision of people with keratoconus, and they also allow people to play sports without having to worry about breaking their glasses.

Coolidge, William David

William Coolidge (1873-1975) was born in Hudson, Massachusetts, the son of a farmer and a dressmaker. As a youth, he worked in a shoe factory to help support his family. After attending public schools, Coolidge funded his

William Coolidge is credited with developing the X-ray tube and the ductile tungsten filament used in modern incandescent electrical lamps.

own college education by borrowing money and earning scholarships and fellowships. With a degree from the Massachusetts Institute of Technology (MIT), Coolidge went to Germany to study physics. After earning his doctoral degree with high honors, he returned to MIT to do research.

Although Coolidge was content at MIT, in 1905 he was lured to General Electric Company's research laboratory with an offer to double his MIT salary. Coolidge had avoided a career in industry after experiencing factory work, but General Electric (GE) promised him freedom to pursue his own interests as well as the company's commercial research goals.

In just a few years, Coolidge solved one of the greatest technological problems of the time—developing a better filament for incandescent (very bright) light bulbs. Early electric light bulbs used carbon filaments, which were not only delicate to handle but also limited in the amount of light they could produce. Scientists knew that tungsten (the metal with the highest melting point), would perform better than carbon, but because tungsten is brittle, no one could figure out a way to make filaments from it. Coolidge invented a process for making tungsten bendable. As a result, modern electric light bulbs are still made with tungsten.

Coolidge also invented an **X-ray** tube that is still used by doctors and dentists. His revolutionary tube was based on a tungsten "target," which is bombarded in a vacuum by a stream of electrons to produce X-rays. Coolidge's tube allowed much more precise control over the X-ray wave length and could also accommodate much higher voltages.

During World War II (1939-1945), Coolidge contributed his expertise to various war-related projects. He postponed his retirement until 1945 in order to work throughout the war. Coolidge lived to the age of 102, continuing to enjoy hobbies such as travel and photography.

Cortisone

Cortisone is one of a family of steroid hormones secreted by the cortex (outer layer) of the adrenal gland, which is located on the kidneys. The

adrenal cortex is the chief organ of homeostasis (the body's ability to remain internally stable even in the presence of stressful changes in the environment, such as extreme cold, hunger, thirst, and danger). The adrenocortical steroids, called corticosteroids or corticoids, are classified according to what they do. Glucocorticoids control sugar metabolism (the continuous process in living organisms in which matter is broken down into simpler units or waste matter), and mineralocorticoids control the metabolism of minerals and water.

The principal glucocorticoids are corticosterone and hydrocortisone (cortisol) and the principal mineralocorticoid is aldosterone. **Cortisone,** originally called compound E, is a glucocorticoid, but also has some mineralocorticoid properties. It quickly converts protein to the carbohydrate glucose (sugar), and it helps regulate salt metabolism. The adrenal cortex's production of cortisone and hydrocortisone is controlled by the hormone **ACTH** (adrenocorticotropic hormone), which is secreted by the pituitary gland (a small, oval gland attached to the base of the brain).

Three scientists won the 1950 Nobel prize in medicine for their work with cortisone and other adrenal hormones. In fact, most of today's information about cortisone is due primarily to the work of Swiss chemist Tadeus Reichstein (1897-) and Americans Edward Calvin Kendall (1886-1972), a biochemist, and Philip Showalter Hench (1896-1965), a medical researcher. Kendall first began work on adrenal cortex hormones because an extract had been used successfully against Addison's disease, which is caused by adrenal gland problems. The original hormone theory, devel-

Cortisone. Cortisone and other corticosteroids are often prescribed to reduce inflammation in bronchial asthma, allergies, arthritis, and other connective tissue diseases.

oped by the British physiologists William Bayliss and Ernest Starling, held that each type of gland secreted (released) only one hormone. By the mid-1930s, however, Kendall and others believed that the adrenal gland produced many hormones. In 1936 Reichstein was the first scientist to isolate the hormone that was later named cortisone, making it the first corticosteroid evere described. Kendall isolated a series of adrenal substances and converted one he called "compound E" into an active substance that he believed to be a **steroid**.

Hench and Kendall studied compound E, thinking it may be useful in treating arthritis because of its anti-inflammatory effect (the ability to prevent or suppress the heat, redness, swelling, and tenderness of inflammation). In 1948 and 1949, Hench and Kendall gave the name cortisone to compound E. The next year Hench and another colleague were the first to use it to successfully treat arthritis.

Corticosteroids Within the Body

Corticosteroids have widespread effects within the body. They influence the metabolism of protein, carbohydrates, and fat, and the functions of the cardiovascular system, the kidneys, skeletal muscle, nervous system, and other organs and tissues. Because of this, they must be used carefully. Long-term corticosteroid treatments have some serious side effects. These include edema (fluid retention), high stomach acidity, slow growth in children, osteoporosis (a bone disease, especially affecting older women, that decreases bone mass and makes bones porous, or full of tiny holes, and weak), and a redistribution of body fat that can result in a disorder called Cushing's syndrome.

Cortisone and other corticosteroids are used mainly in the treatment of deficiencies in the pituitary-adrenal complex. For example, they are used as replacement hormones in Addison's disease, and for people whose adrenal glands have been removed. They are also prescribed to reduce inflammation (swelling) in bronchial asthma, allergies, arthritis, and other connective tissue diseases. Other uses include therapy for some types of kidney disease, diseases resulting in inflammation of the eye, skin irritations, and some diseases of the intestinal tract. Glucocorticoids can be used in some types of cancer therapy, and the glucocorticoid prednisone is used with the drug cyclosporine to help reduce the body's immune response and prevent rejection of transplanted organs.

Scientists have experimented to produce synthetic steroids that can be more specifically prescribed. These synthetics act more specifically to

treat the patient without affecting his or her entire hormonal balance. They have replaced natural corticosteroids in many instances.

[*See also* **Cyclosporine; Hormone; Steroids**]

Crick, Francis Harry Compton

Francis Harry Compton Crick (1916-) worked closely with **James Dewey Watson** (1928-) to work out the structure of the deoxyribonucleic acid (DNA) molecule. This research was very important because it showed that DNA was the true carrier of genetic instructions in cells. Crick was born in 1916 in Northampton, England. After graduating with a degree in physics from University College (London), he developed radar systems and magnetic mines for the British military during World War II (1939-1945). In 1947, he worked at Strangeways Research Laboratory by day and studied biology in the evenings. Crick later moved to the Cavendish Laboratory at Cambridge University. It was there that he first met Watson and began work on the structure of DNA. Although Watson had to initially persuade him to take up the DNA project, it was not long before Crick became an enthusiastic participant. For their DNA studies, Crick and Watson—along with Maurice Hugh Frederick Wilkins (1916-)—were awarded the Nobel Prize in 1963.

Francis Harry Compton Crick.

In 1977 Crick's distinguished status in the scientific community earned him a professorship at the famous Salk Institute for Biological Studies in San Diego, California. He continues to lead an active role in several areas of ongoing research today, particularly the nature of consciousness and the workings of the brain.

[*See also* **Gene**]

Cryogenics

Cryogenics is the study and use of materials at extremely low temperatures. Such low temperatures cause changes in the physical properties of materials that allow them to be used in unusual engineering, industrial, and medical applica-

tions. For example, in the cryogenic temperature range, air becomes a liquid—or even a solid—and living tissue freezes instantly. Matter behaves strangely at the lowest temperatures of the cryogenic range. Electric currents never stop flowing, liquids run uphill, and rubber becomes as brittle as glass. In medicine, cryogenic cooling is used in some diagnostic techniques, such as **magnetic resonance imaging** (MRI). Cryosurgery uses liquid nitrogen to kill unhealthy tissue by freezing it. Cryogenics is expected to play an important role in the development of better procedures for preserving human organs for **transplant.**

Cryogenics is expected to play an important role in the development of better procedures for preserving human organs for transplant.

Early Research

British chemists Michael Faraday (1791-1867) and **Sir Humphry Davy** (1778-1829) did pioneering work in low-temperature physics that led to the development of cryogenics. In the early to middle 1800s they were able to produce gases by heating mixtures at one end of a sealed tube in the shape of an inverted "V." A salt and ice mixture was used to cool the other end of the tube. This combination of reduced temperature and increased pressure caused the gas that was produced to liquefy (turn to a liguid). When they opened the tube, the liquid quickly evaporated and cooled to its normal boiling point.

In 1877, French mining engineer Louis Paul Cailletet announced that he had liquefied oxygen and nitrogen. Cailletet was able to produce only a few droplets of these liquefied gases, however. In his research with oxygen, Cailletet collected the oxygen in a sturdy container and cooled it by evaporating (drying up) sulphur dioxide in contact with the container. He then compressed the oxygen as much as possible with his equipment. Next he reduced the pressure suddenly, causing the oxygen to expand. The sudden cooling that resulted caused a few drops of liquid oxygen to form.

The need for a way to store liquefied gases led to another important development in cryogenics. In 1891 Scottish chemist James Dewar (1842-1923) inroduced the container known today as the "Dewar flask." The Dewar flask is actually two flasks, one within the other, separated by an evacuated space (a vacuum). The inside of the outer flask and the outside of the inner flask are coated with silver. The vacuum and the silvered sides of the container are designed to prevent heat passage.

Dewar was also the first person to liquefy hydrogen in 1898. In 1908 Dutch physicist Heike Kamerlingh Onnes (1853-1926; 1913 Nobel Prize winner for physics) liquefied the most difficult gas of all, helium. He liquefied it at the lowest temperature ever achieved in a laboratory to that date, 4.2 kelvins (the kelvin measurement is a scale of temperatures measured in degrees Celcius from absolute zero). This marked a significant

milestone in the history of cryogenics. Since that achievement, increased attention has been devoted to the study of physical phenomena of substances at very low temperatures.

The Cooling Process

A substance is normally cooled by placing it next to something colder. To make the substance supercold, however, heat must also be removed and the substance must be insulated (encased). An important method of cryogenic supercooling involves liquefying gases and using these gases to cool other substances. One technique is to convert to liquid form a gas that can be liquefied by pressure alone. Then a gas requiring a lower temperature to become a liquid is placed in a container and immersed (dipped) in the first. The gas that is already liquefied cools the second and converts it to a liquid. After several repetitions of this process, the targeted gas is liquefied. A Dewar flask is normally used to store such very low temperature liquefied gases.

Since the 1930s, cryogenic cooling has most often been achieved through magnetic means. In 1926, Canadian chemist William Francis Giauque theorized that if the disorderly spin of electrons in a substance could be slowed down, then the substance would cool down. His experiments proved this theory. In cooling by demagnetization, a strong magnetic force is used to give the outside energy required to line up the molecules of a paramagnetic substance (one made up of paramagnetic ions). This also raises the temperature. At the same time the substance is cooled in liquid helium. When the substance cools down to its starting temperature, the magnetic field is removed. This causes the ions to resume their disorderly align-

Doctors prepare a patient for cryogenic surgery.

ment (order). The energy the ions use to move comes from the heat energy of the substance, which causes the temperature of the substance to drop.

Liquid nitrogen is one of the safest cooling agents available. In medicine it is used to kill unhealthy tissues by freezing them. Cryogenic processes are also used to supply "banks" storing eye corneas, blood, and sperm for future surgical procedures. Some embryos have also been frozen and stored for later implantation (surgical placement) in women.

Cryogenic processes are used to supply "banks" storing eye corneas, blood, and sperm for future surgical procedures.

Cryosurgery

In 1961 American surgeon Irving S. Cooper introduced a freezing technique called cryosurgery. Cryosurgery is relatively bloodless because the low temperatures used constrict the blood vessels, stemming the flow. Special instruments are used that have freezing tips to kill the damaged tissue and shields to protect surrounding tissue. Cooper used cryosurgery to freeze and destroy damaged tissue in the brains of patients with Parkinson's disease (a degenerative illness). Since then, cryosurgery has found many applications. It is used to repair detached retinas and to remove cataracts. It is also used to treat liver cancer and prostate cancer.

Cryosurgery is also widely used in the fields of dermatology, gynecology, plastic surgery, orthopedics, and podiatry. Cryosurgery has also been used successfully for more than 30 years in veterinary medicine.

Curare

Curare is a name used to identify a variety of highly toxic (poisonous) extracts from some types of woody vines that grow in South America. European scientists began studying curare in the late sixteenth century after explorers learned that Indians living along the Amazon and Orinoco Rivers in South America had been using it for centuries to make poison-tipped hunting arrows. The poison in the arrows killed animals by paralyzing (numbing) their muscles. When the muscles used for breathing became paralyzed, the animals died of suffocation. These deadly arrows were sometimes used against the European explorers and soldiers. Natives called the poisonous plant ourari (or "woorari"), which became "curare" to the Europeans.

In 1735 a scientific expedition sponsored by the French Academy of Sciences was sent to the area of South America that is now Ecuador. Heading the expedition was the Frenchman Charles Marie de la Condamine,

who spent part of ten years in South America scientifically exploring the region. La Condamine collected samples of curare and took them back to France.

During the nineteenth century, doctors tried to use curare as a muscle relaxant in the treatment of rabies, tetanus (an infectious disease that usually enters the body through a wound), and epilepsy (a chronic, or lasting, disease of the nervous system characterized by convulsions), but these trials were unsuccessful because available curare extracts were not of equal quality and potency (strength). In the 1870s curare was used to keep conscious animals from moving during experimental surgery. This practice angered many people in Great Britain and led to the passage of anti-vivisection laws (laws against using animals for scientific experimentation).

The first breakthrough leading to successful medical use of curare came in 1935, when Harold King isolated its active principle, which he called tubocurarine. A chemically pure alkaloid (an organic base of a plant, containing nitrogen and usually oxygen) of curare was introduced in 1942 by Thomas Cullen. This purified alkaloid is called d-tubocurarine. Curare contains two alkaloids: curine, which paralyzes the muscle fibers of the heart, and curarine, which paralyzes the motor nerve endings in voluntary muscles.

That same year, a country doctor and part-time anesthetist named Harold Griffith of Montreal, Quebec, tested the use of curare in surgery. He used it as a muscle relaxant that let him use lower, safer doses of **anesthesia.** Over the next ten years, many doctors began using curare to relax their patients' muscles during abdominal surgery or during tracheal intubation (the inserting of a tube into the trachea to allow a patient to breathe).

Artificial Curare

Because the effects of natural curare were still unpredictable, Swiss-Italian pharmacologist Daniele Bovet (1907-1992; winner of the 1957 Nobel Prize in medicine) of the Pasteur Institute in Paris, France, set out to make a synthetic (artificially produced) uniform curare. He succeeded in 1947 with the medicine gallamine, and then went on to make more than 400 compounds that had the same effects as curare. One of these compounds, succinylcholine, became a widely used and effective curare substitute that could be given in precise dosages with predictable effects. Succinylcholine allows complete muscle relaxation during surgery without deep anesthesia.

While d-tubocurarine and similar compounds totally paralyze the muscles, they do not affect the central nervous system. A patient who

receives an injection (shot) of this drug into a muscle quickly begins to feel dizzy and warm. The muscles of the jaw, neck, and head are the first to become weak and relaxed. The person can hear low tones better because small muscles in the middle ear relax. Then the arms and legs begin to feel heavy and difficult to move. Breathing becomes harder, and the patient experiences "shortness of breath," even with artificial respiration. He cannot swallow and feels like he is choking because saliva accumulates in the throat. Soon it is impossible to move at all. During this time the patient is fully conscious of everything around him and can sense pain. For this reason anesthesia is still needed during medical procedures, though in smaller amounts.

The effects of curare do not last long, and a person or animal who has been poisoned by this substance can fully recover if given artificial respiration until the poison wears off. The action of d-tubocurarine or its related compounds like succinylcholine begins to wear off after about 20 minutes if a single moderate dose is injected into a vein, the usual method of giving the drug. During surgery the patient may have to be given additional small doses of d-tubocurarine. The drug has little or no effect if taken by mouth, unless swallowed in very large doses.

Curare-like drugs are sometimes used to relax muscles when doctors are correcting dislocations or setting bone fractures, and in the control of muscle spasms during convulsions like those seen with tetanus, epilepsy, drug overdose, and following the bite of the black widow spider. These drugs are also used during tracheal intubation, and to help make examinations of the larynx, bronchial tubes, and esophagus easier.

Curie, Marie

Marie Curie's contribution to the field of medicine is overshadowed by her initial discovery of two radioactive elements, polonium and radium.

Marie Curie's (1867-1934) amazing persistence in the face of many research obstacles is enough to commend her to historical fame. Her contribution to the field of medicine is overshadowed by her initial discovery of two radioactive elements, polonium and radium. She used these discoveries to help develop therapies for disease.

Curie was born Marie Sklodowska in Warsaw, Poland, in 1867. Her mother was principal of a local girls' school, and her father was a physics teacher. Curie excelled at school and was encouraged in her studies by her parents. Unfortunately, Poland was under Russian rule, and Russian authorities did not want educated Poles to become politically active and

possibly lead a rebellion. As a result, Curie was not allowed to go to college in Poland. After working for several years, she left Poland for France, where she enrolled at the Sorbonne in 1891. Her meager savings barely covered tuition and rent for her one-room apartment, and she often went for long periods without food and once fainted from hunger during class. Her enthusiasm for learning did not waver, however, and in 1893 she received a degree in physics, graduating first in her class. While pursuing a second degree, she met Pierre Curie, who had made a name for himself by discovering piezoelectricity a few years earlier. The couple was married on July 26, 1895.

Soon after the marriage, Pierre earned his doctorate. Marie was still working toward her dissertation, but had not chosen a topic. French physicist Antoine Henri Becquerel (1852-1908; first scientist to experiment with radioactivity) had just discovered that uranium salts emitted (gave off) energy. At his suggestion, Marie set out to find other substances that emitted such rays. It was known that the ore pitchblende possessed properties similar to those of uranium, so the Curies chose this ore as the starting point for their research.

Research Leads to Results

Within the pitchblende the Curies detected the presence of a substance that was much more radioactive (a word Marie Curie had coined, or made up) than even pure uranium. They extracted (pulled out) this new element in 1898 and named it polonium, after Marie Curie's homeland of Poland. Although the polonium discovery was quite significant, the Curies were not satisfied. They could tell from their tests that another element, thousands of times more radioactive than uranium, existed in the pitchblende, but in such small amounts as to be nearly undetectable. Another French chemist confirmed the presence of this element—which the Curies had named radium—by examining pitchblende's spectral (wide band) lines. This did not convince many scientists, nor did it satisfy the Curies, who were determined to prove the existence of radium by extracting a measurable amount. This would be no small task, since several tons of pitchblende would have to be refined in order to produce even a gram of radium.

Marie Curie.

Pierre Curie abandoned his teaching position in order to assist his wife's research. Though Marie Curie was the engine and mastermind of the project, she and her husband worked as a team. In fact, all of the notes in her dissertation refer to the experimenters as "we"—neither she nor her husband are mentioned individually.

The Curies spent the bulk of their life savings to purchase waste ore from Czechoslovakian mines. They rented a leaky wooden shed in which they could refine the raw ore, and for the next four years they refined and purified the pitchblende, producing smaller and smaller samples that were more and more radioactive. The exhausting process, ordinarily performed by a team of several mine workers, took a physical toll upon the couple. This work, along with the birth of their daughter Irene, was nearly too much for the couple. Only Marie's intense determination kept things going. By 1902 the Curies had extracted one-tenth of a gram of radium, enough for Marie to finish her dissertation.

The Curies and Becquerel shared the 1903 Nobel Prize in physics for their contributions to the new science of radioactivity. Pierre Curie was also offered a professorial position in the Sorbonne's research laboratory, an offer that included his wife coming along as his lab superintendent. In 1906, however, tragedy struck when Pierre Curie was crushed to death in a traffic accident. Marie took over his position and continued his lectures at the exact point at which they were interrupted. She was the first woman to teach at the Sorbonne.

Working Alone

In the years after her husband's death, Curie conducted extensive work at the new Paris Institute of Radium. In spite of its mysterious properties, radium was used as a medicinal aid. Though it was often used without thought to its dangers or effectiveness, Curie proved that there were certain illnesses for which radium was effective. It played an important role in the treatment of cancer, and is still used for this purpose today. Curie also introduced the use of radium and **X-ray** technology in medicine. For the discovery of radium and polonium, Curie was awarded the 1911 Nobel Prize in chemistry, becoming the only person to hold two Nobel laureates in the sciences.

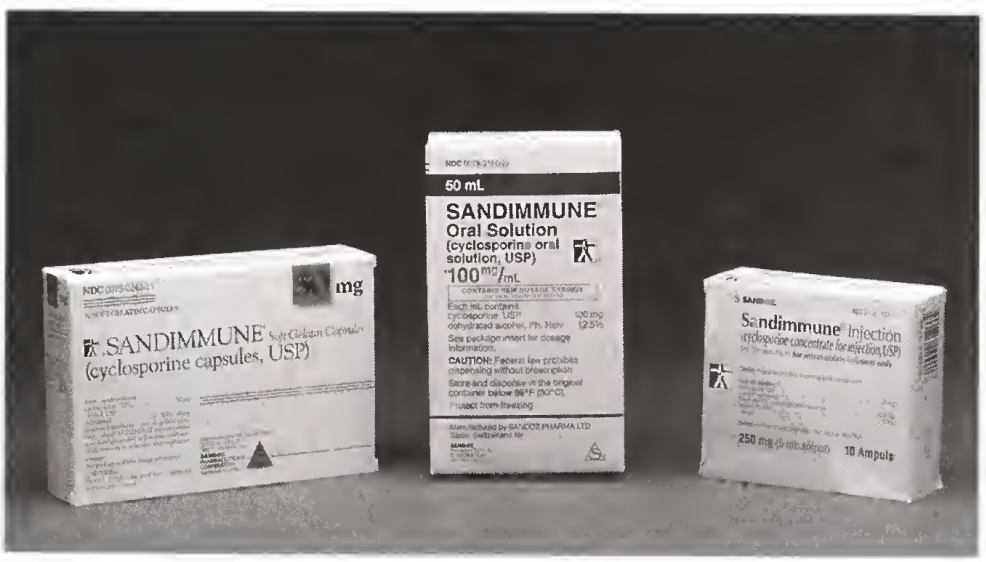
Except for World War I (1914-1918), during which she drove an **ambulance,** Curie spent the remainder of her life studying radium therapy. Though the process was successful, she received no royalties from its use, since she and her husband had chosen not to make money from their discovery by patenting (registering) it. Late in Curie's life, the dangerous

nature of radioactivity took a personal toll. Curie's long years of exposure to radium resulted in leukemia (a disease that effects blood-forming organs), which lead to her death in 1934. Today, Curie is historically remembered as an outstanding female scientist, as well as one of the world's greatest researchers.

Cyclosporine

Cyclosporine is a drug obtained from a type of soil fungus found in Norway called Tolypocladium inflatum. The drug is valuable in organ **transplants** because it suppresses the action of certain cells in the body's immune (disease-fighting) system that can reject the transplanted organ. While preventing attacks of these cells, called T cells (or T-helper cells), cyclosporine lets the bulk of the body's immune system function normally and fight general infection.

Cyclosporine is a relatively new drug. It was approved by the U.S. Food and Drug Administration in 1983 for use in all transplant patients. Before the use of cyclosporine, live organs could be transplanted from one body to another, but the drugs necessary to prevent rejection of the foreign tissue weakened the patient's entire immune system. Frequently patients could not survive the severe infections that followed transplants, and mortality (death) rates for transplant patients were discouragingly high. The discovery of cyclosporine brought about a major shift in the success of transplantation.



Cyclosporine lets the bulk of the body's immune system function normally and fight general infection.

Borel's Studies

Jean-Francois Borel (1934-), a microbiologist working for Sandoz Laboratories in Switzerland, discovered cyclosporine in 1969 when he was vacationing in Norway. Sandoz employees were encouraged to gather samples of naturally occurring organisms for analysis in the laboratory. When Borel visited Hardanger Vidda, a desolate highland plateau in southern Norway, he collected some soil samples and brought them back to Sandoz for testing.

Sandoz Laboratories was involved primarily in **antibiotics** research, and the purpose of their first series of tests on cyclosporine was to determine the substance's potential as an antibiotic. The tests yielded little of interest as far as antibiotics were concerned, but did show that cyclosporine had distinct immunosuppressive capabilities. Since his doctoral studies involved immunogenetics (the study of how the immune system works), Borel decided that he wanted to learn more about cyclosporine.

Borel ran a second series of tests and found that cyclosporine inhibits the activity of lymphocytes (white blood cells), the part of the immune system that starts the process of detecting and attacking foreign invaders. Lymphocytes aid in the formation of cytotoxic (toxic to cells) T cells. These cells, along with blood cells called monocytes and macrophages, are thought to be responsible for the rejection of transplanted organs. Cyclosporine does not actually destroy the T cells, but fends them off. It acts at an early stage in the life cycle of the T cell, inhibiting its action by blocking the intercellular message carried by a cellular compound called interleukin-2.

A Disappointing Setback

It looked as if Borel had discovered a superior drug for transplantation, but his employer was not sufficiently impressed by the findings he reported in 1972. The estimated costs for production and testing of the drug were too high, and organ transplantation was just getting started. The potential demand for cyclosporine was questionable. Sandoz was unwilling to put the necessary money and energy behind the drug for further exploration.

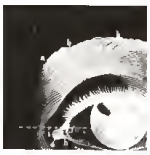
Two immunologists recognized the importance of Borel's discovery, however, when the researcher presented his results to the British Society of Immunologists in 1976. David White and Sir Roy Calne asked Borel for samples of cyclosporine and began their own clinical studies using organ transplantation in rats. The results were remarkable: rejection was almost nonexistent, and the survival rate was far better than for other immunosuppressants. In mid-1977, White and Calne informed Borel of their find-

ings and requested more samples of cyclosporine to continue their clinical trials, this time on dogs. Borel, hoping to revive Sandoz's interest in cyclosporine, asked White and Calne to present their findings to Sandoz. The pharmaceutical company agreed that the drug looked much more promising now that there was evidence of its effectiveness.

The success of cyclosporine suffered a setback in 1979 when further studies showed it to be nephrotoxic (poisonous to the kidneys) and to cause lymphomas (tumors). These side effects proved to be the result of high doses of the drug. The practice at the time was to administer as much cyclosporine as the body could handle, short of a toxic level. Research later showed it should be given in small amounts, just enough cyclosporine to prevent rejection of a transplanted organ. With the decreased dosage, the lymphoma was eliminated and nephrotoxicity was reduced.

Later research by Thomas Starzl in Colorado indicated that cyclosporine worked most effectively when administered with **steroids.** In 1983 the Food and Drug Administration approved cyclosporine for use in all transplant patients ,but said it must be given only in conjunction with steroids. Cyclosporine must be taken indefinitely by persons who have received organ transplants, however, and the possibility of irreversible kidney failure remains a serious concern.

Cyclosporine is not a perfect drug, but it is the most potent (strong) and specific immunosuppressant available for organ transplant patients. It is effective in treating infections after the surgery, and it is associated with a lower mortality rate among transplant patients. It is commonly used in kidney, heart and lung, liver and pancreas, and bone marrow transplants. Cyclosporine is also used to treat viral and fungal infections and immune disorders, to promote healing of wounds, and in certain kinds of tissue grafts. The drug is also used in treating certain autoimmune diseases such as myasthenia gravis and is being tested for use in treating inflammatory bowel disease.



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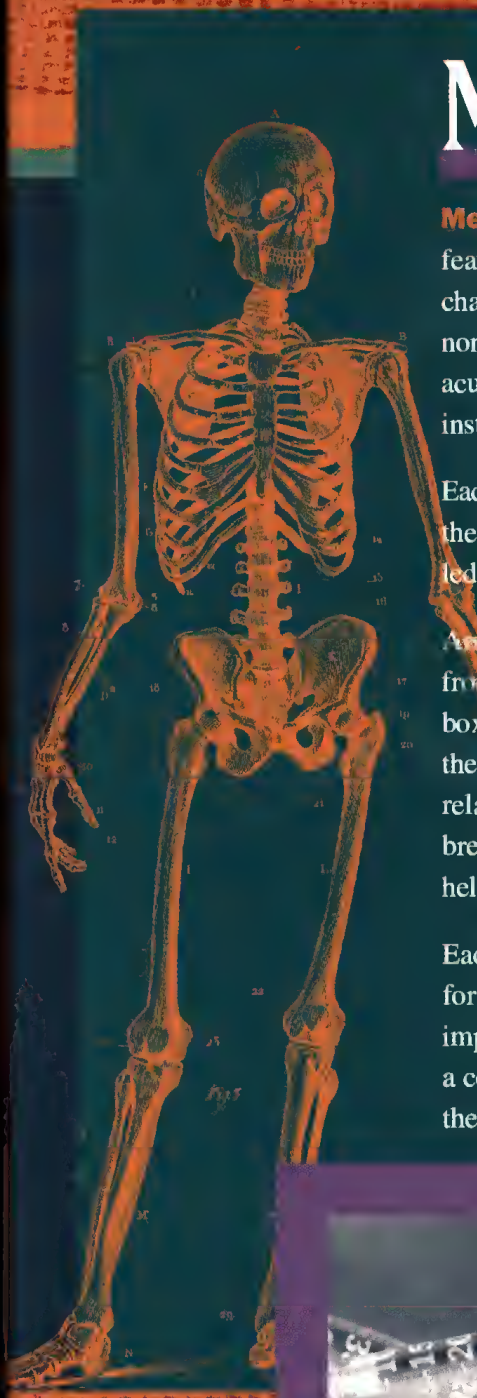


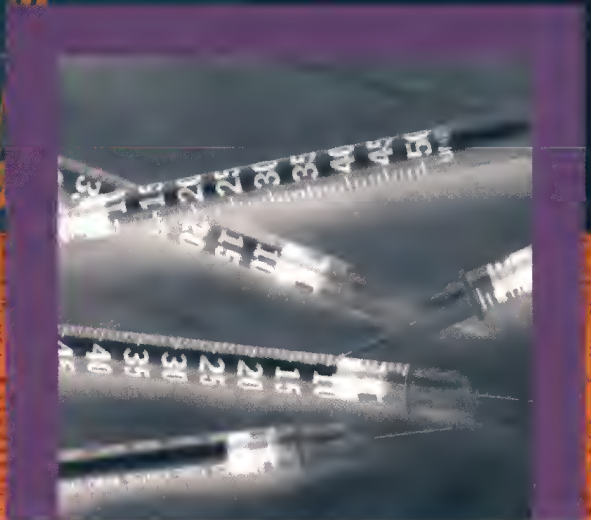
Medical Discoveries:

Medical Breakthroughs and the People Who Developed Them features 215 medical and dental inventions and discoveries that have profoundly changed the way diseases are diagnosed and people are treated. Written in nontechnical language, *Medical Discoveries* explores medical practices such as acupuncture, significant developments in research such as chemotherapy, and instrumentation such as the X-ray machine.

Each entry, whether on a well-known discovery or lesser-known invention, identifies the person behind the breakthrough, explores the knowledge and technology that led to it, and explains how the advance changed the world in which we live.

Arranged alphabetically over three volumes, *Medical Discoveries'* entries range from one-quarter to six pages in length. Accompanying several entries are sidebar boxes discussing related topics and items of special interest to students, such as the discovery of DNA structure. Boldfaced terms in the text direct students to related entries, while cross-references at the end of entries direct readers to other breakthroughs that might be of interest. More than 150 photographs enliven and help explain the text.

Each volume opens with a further readings page that directs students to sources for further study, a timeline of medical and dental landmarks, and a glossary of important medical and dental terms found in the text. The volumes conclude with a comprehensive general index that allows students quick access to the people, theories, and inventions discussed in *Medical Discoveries*.



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